

BLA Clinical Review Memorandum

Application Type	Original
STN	125807/0
CBER Received Date	September 25, 2023
PDUFA Goal Date	April 29, 2025
Division / Office	Division of Clinical Evaluation General Medicine (DCEGM) / Office of Clinical Evaluation (OCE)
Priority Review (Yes/No)	Yes
Review Completion Date	April 29, 2025
Review Team	
Clinical Reviewer	Chinwe N. Okoro, MD
Clinical Pharmacology Reviewer	Yang Chang, Ph.D., Pharm.D.
Labeling Reviewer	Afsah Amin, MD, MPH
Clinical Team Leader	Vijay Kumar, MD
Division Director	Patroula Smpokou, MD
Applicant	Abeona Therapeutics Inc
Established Name	Prademagene Zamikeracel (PZ) or EB-101
(Proposed) Trade Name	ZEVASKYN
Pharmacologic Class	(b) (4) virus derived retroviral vector (LZRSE) autologous cell sheet-based gene therapy
Formulation(s), including Adjuvants, etc.	PZ is a rectangular cell sheet, attached to a petrolatum gauze backing with titanium ligating clips.
Dosage Form(s) and Route(s) of Administration	One sheet of ZEVASKYN covers an area of 41.25 cm ² . Surgical topical application on wounds with sutures.
Dosing Regimen	Recommended dose of ZEVASKYN is based on the surface area of the wound(s).
Proposed Indication(s) and Intended Population(s)	Treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB)
Orphan Designated (Yes/No)	Yes

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Glossary

AE	adverse event
AF	anchoring fibril
BLA	biologics license application
COL7, C7	human type VII collagen
COL7A1	collagen type VII alpha 1 chain
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
EB	epidermolysis bullosa
FDA	U.S. Food and Drug Administration
ICF	informed consent form
IF	immunofluorescence
IIF	indirect immunofluorescence
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
LZRSE	(b) (4) virus derived retroviral vector
LTFU	long-term follow-up
NRS	Numeric Rating Scale
PD	pharmacodynamic
PI	prescribing information
PMR	post marketing requirement
RCR	Replication Competent Retrovirus
RDEB	recessive dystrophic epidermolysis bullosa
REMS	Risk Evaluation and Mitigation Strategies
SAE	serious adverse event
SOC	Standard of Care
SCC	squamous cell carcinoma
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information

1. EXECUTIVE SUMMARY

On September 25, 2023, Abeona Therapeutics Inc (the Applicant) submitted a Biologics License Application (BLA) 125807 for Prademagene Zamikeracel (Proprietary name: ZEVASKYN, referred in the submission as PZ or EB-101). The Applicant requests approval for the following proposed indication: treatment of large, chronic wounds (defined as wounds with $\geq 20\text{cm}^2$ surface area with a duration of ≥ 6 months), in subjects ≥ 6 years of age with recessive dystrophic epidermolysis bullosa (RDEB).

Dystrophic epidermolysis bullosa (DEB) is a genetic skin disorder affecting skin and nails that usually presents at birth. Recessive dystrophic epidermolysis bullosa (RDEB) is an ultra-rare, life-threatening form of DEB characterized by skin fragility manifesting as skin blistering with minimal trauma which heals with milia and scarring.

EB-101 consists of a one to three cell layer thick sheet, composed of autologous cells from a skin biopsy that have been transduced *ex vivo* with a (b) (4) virus derived retroviral vector (LZRSE) that contains the full-length human collagen type VII alpha 1 chain (COL7A1) gene (LZRSE-COL7A1) to form gene-corrected epidermal sheets that express biologically active type VII collagen (C7) protein. After EB-101 is applied onto the open wounds of the corresponding patient with RDEB the C7 protein is expressed at the wound site.

Study EB- 101-CL-301 (Study 1), a phase 3, multicenter, randomized, intra-patient-controlled study of EB-101 in 11 patients with RDEB met both co-primary endpoints showing statistically and clinically significant results on wound healing and pain reduction and provides the primary evidence of effectiveness. A phase 1/2, exploratory study of EB-101 showed similarly favorable results on wound healing in a different population of patients with RDEB and provides supportive and confirmatory evidence. No serious adverse events were attributed to EB-101 treatment and the most common adverse events were wound infection, pruritus, immune reaction and procedural pain. Expression of COL7 and presence of anchoring fibrils (AFs) were demonstrated in 6 patients at 3 months, 5 patients at 6 months and 3 patients at one year. The PD data supported the primary efficacy endpoints. Circulating anti-C7 antibodies were observed in 2 patients and tissue-bound antibodies beyond trace staining were detected in 4 patients. In study EB-101-CL-301, all patient biopsies were negative for C7 immune complexes, and no systemic immunologic responses were reported. There was no significant impact of anti-C7 antibodies on efficacy. However, data are limited to fully evaluate the impact of anti-C7 antibodies on clinical outcome and PD activity. In addition, all patients tested negative for replication competent retrovirus (RCR).

The EB-101 clinical development program included patients ≥ 6 years of age with RDEB. The review team determined it is appropriate to extrapolate the efficacy and safety demonstrated in the studied population to pediatric patients younger than 6 years of age for the following reasons:

- a. The wounds observed in children are similar to those observed in adults in RDEB. RDEB is a monogenic disease with similar manifestations across age groups and with the same pathophysiology. The response to treatment with EB-

101 is expected to be similar across patients of different ages as the therapy is applied locally.

- b. The product dose is based on wound surface area as it is topically administered. Dosing is independent of age, weight, or body surface area. Therefore, no differences in dosing are expected across different ages.
- c. Efficacy assessments were the same in the adult treated population as was the pediatric population. There are no different considerations in assessing efficacy in younger children (younger than 6 years old) as compared to older children and adults.
- d. No serious safety signals were identified in dosed patients (children over 6 years old and adults) that warrants additional safety measures in younger children.

In summary, The Applicant has provided substantial evidence of effectiveness for EB-101 in pediatric and adult patients with RDEB based on a single adequate and well controlled randomized, phase 3 study accompanied by confirmatory evidence from the mechanism of action of the product in addition to supportive efficacy data from an early, exploratory study. The studied population included adults and pediatric patients 6 years old and older. RDEB is a monogenic disease and the disease pathophysiology/progression and response to treatment is expected to be similar across RDEB patients of different ages. Therefore, it is scientifically reasonable to extrapolate efficacy and safety from older pediatric patients and adults to younger pediatric patients (younger than 6 years of age).

Recommended Regulatory Action

Based on our clinical evaluation, the demonstrated benefits of EB-101 outweigh the observed risks and the benefit-risk assessment is favorable. The review team recommends approval of EB-101 for the treatment of wounds in adult and pediatric patients with RDEB.

1.1 Patient Experience Data

None

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	Section 6
<input checked="" type="checkbox"/>	Observer-reported outcome	Section 6
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease Studied

Epidermolysis bullosa (EB) is a heterogeneous group of inherited mechanobullous disorders caused by mutations in genes that encode structural proteins in the skin. There are 3 major subtypes characterized by a distinct plane of epidermal-dermal separation following minor trauma: simplex EB (EBS), junctional EB (JEB) and dystrophic EB (DEB).

DEB is divided into two major types depending on the pattern of inheritance, a dominant milder type (DDEB) and a more devastating recessive type (RDEB). Both RDEB and

DDEB have multiple subtypes based on the type of *COL7A1* mutation involved, resulting in a wide spectrum of clinical severity. Both forms involve a mutation in the *COL7A1* gene, which encodes type VII collagen (C7), a structural component of AFs which hold the epidermis and dermis together and are essential for maintaining the integrity of the skin. Mutation in C7 results in poor epidermal-dermal adherence.

The diagnosis of DEB is established in a proband with characteristic clinical findings and the identification of biallelic pathogenic variants (RDEB) or a heterozygous pathogenic variant (DDEB) in *COL7A1* by molecular genetic testing. If molecular genetic testing is not diagnostic, examination of a skin biopsy with direct immunofluorescence (IF) for specific cutaneous markers and/or electron microscopy (EM) may be necessary for diagnosis. Absence of a known family history of DEB does not preclude the diagnosis.

Clinical findings in severe generalized RDEB include skin fragility manifest by blistering with minimal trauma that heals with milia and scarring. Blistering and erosions affecting the whole body may be present in the neonatal period. Oral involvement may lead to mouth blistering, fusion of the tongue to the floor of the mouth, and progressive diminution of the size of the oral cavity. Esophageal erosions can lead to webs and strictures that can cause severe dysphagia. In DDEB, blistering is often mild and limited to hands, feet, knees, and elbows, but nonetheless heals with scarring. Dystrophic nails, especially toenails, are common and may be the only manifestation of DDEB.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

FDA recently approved two products for the treatment of RDEB. VYJUVEK® (beremagene geperpavec-svdt), a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy indicated for the treatment of wounds in patients six months of age and older with DEB with mutation(s) in the collagen type VII alpha 1 chain (*COL7A1*) gene, was approved in May 2023. FILSUEZ (birch triterpenes), a botanical drug product for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in adult and pediatric patients 6 months of age and older, was approved in October 2023. Prior to VYJUVEK and FILSUEZ approval, treatment of DEB was limited to supportive therapy which include wound care with dressings and padding to protect bony prominences from blister-inducing impact and preventative measures such as avoidance of activities to reduce trauma to the skin that cause minimal trauma to the skin. For infants and children with poor growth may require nutritional support, including feeding gastrostomy. Regular screening for nutritional deficiencies of iron, zinc, vitamin D, selenium, and carnitine may require vitamin and mineral supplementation. Occupational therapy may help prevent hand contractures, or surgical release of fingers may need to be repeated. Beginning in the second decade of life, surveillance for SCC is required for abnormal-appearing wounds that do not heal or have exuberant scar tissue. Yearly echocardiograms to identify dilated cardiomyopathy and bone mineral density studies to identify osteoporosis are also recommended.

Other novel therapies for treatment of RDEB such as bone marrow stem cell therapy and protein therapy have demonstrated success in clinical trials but with limitations such

as immune response from preconditioning regimen and repeated treatments due to degradation.

2.3 Safety and Efficacy of Pharmacologically Related Products

VYJUVEK is a novel HSV-1 vector-based gene therapy product. The safety data of VYJUVEK gel was demonstrated in a randomized, intra-subject placebo-controlled study. A total of 31 subjects with DEB, including 30 subjects with autosomal recessive DEB and one subject with autosomal dominant DEB received topical administration of VYJUVEK gel to their wounds. The age of the subjects ranged from 1 year to 44 years (mean age 17 years). Of the 31 subjects, 19 (61%) were pediatric subjects (less than 17 years of age), and 11 (36%) were females. Each subject received weekly topical application of VYJUVEK gel at one or more wound sites and placebo at a matching wound site as an intra-subject comparator. The median duration of exposure to VYJUVEK gel was 25 weeks. The most frequent adverse reactions (incidence >5%) observed in the study were itching, chills, redness, rash, cough and runny nose. There were no discontinuations due to adverse reactions.

FILSUVEZ (birch triterpenes) is a botanical drug product for the treatment of wounds associated with DEB and junctional epidermolysis bullosa (JEB) in adult and pediatric patients 6 months of age and older. The efficacy and safety of FILSUVEZ was evaluated in a randomized, double-blind, multicenter, placebo-controlled trial in 223 adult and pediatric subjects with inherited EB. Subjects were randomized 1:1 to receive FILSUVEZ (n=109) or placebo topical gel (n=114). The FILSUVEZ group were instructed to apply approximately 1 mm (0.04 inch) of FILSUVEZ to the target wounds at each dressing change (every 1 to 4 days) for 90 days. The target wound was defined as a partial thickness wound of 10-50 cm² in surface area and present for 21 days to 9 months prior to screening. Of the 223 subjects randomized, the median age was 12 years (range: 6 months to 81 years), 70% were under 18 years of age, and 60% were male and 40% were female. One hundred ninety-five (195) had DEB, of which 175 subjects had RDEB and 20 had dominant DEB (DDEB); in addition, there were 26 subjects with JEB and 2 subjects with EB simplex. The most common (incidence ≥2%) adverse reactions is application site reactions.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

VYJUVEK and FILSUVEZ are approved in the United States.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

FDA engaged and corresponded with the Applicant on multiple occasions before and after the Investigational New Drug (IND) application and BLA submission. Major regulatory milestones are summarized in Table 1.

Table 1. Major Regulatory Milestones Correspondence

May 2008	Initial IND submission
August 2009	Clinical Hold removed
May 24, 2017	Granted Orphan Drug Designation (ODD)
May 25, 2017	Rare Pediatric Disease Designation (RPDD)
August 16, 2017	Breakthrough Therapy Designation (BTD)
January 26, 2018	Regenerative Medicine Advanced Therapy (RMAT)
August 25, 2023	Pre-BLA meeting
November 9, 2023	BLA filed, granted Priority Review
January 21, 2024	BLA 120-Day Safety and Efficacy Update received
April 16, 2024	Complete Response (CR) letter issued
October 28, 2024	Resubmission BLA (Class 2)
November 8, 2024	Resubmission acknowledged
April 29, 2025	PDUFA Action goal date for resubmission

Source: The reviewer.

Abbreviations: BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; DEB, Dystrophic Epidermolysis Bullosa; IND, Investigational New Drug application; PDUFA, Prescription Drug User Fee Act; RDEB, Recessive Dystrophic Epidermolysis Bullosa; RMAT, Regenerative Medicine Advanced Therapy

FDA granted EB-101 Rare Pediatric Disease Designation for treatment of dystrophic epidermolysis bullosa (DEB) on May 25, 2017. EB-101 received Regenerative Medicine Advanced Therapy Designation (RMAT) on January 26, 2018, and Breakthrough Therapy Designation on August 16, 2017- both designations for treatment of RDEB. A pre-BLA meeting was held on August 25, 2023.

On April 16th, 2024, a Complete Response letter was issued to the Applicant due to chemistry, manufacturing, and controls (CMC) concerns with EB-101. Please see CMC review memo for details.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. The BLA was filed on September 25, 2023.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Both the Phase 1/2a and Phase 3 study enrolled subjects in the U.S and were conducted under IND 13708. The Institutional Review Board (IRB)/Ethics Committee (EC) at each investigational site reviewed and approved the protocol and informed consent form (ICF) for the study prior to site initiation in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Amendments to the protocol and ICF were also reviewed and approved by the IRB/EC. All patient recruitment and advertising information was submitted to the IRB/EC and Abeona Therapeutics prior to implementation. A copy of written IRB/EC approval of the protocol and ICF was provided to Abeona Therapeutics prior to initiation of the study. Study treatment was not shipped to the Investigator until Abeona Therapeutics, or its designee had received a copy of the letter or certificate of approval from the IRB/EC for the protocol.

During the BLA review, routine Bioresearch Monitoring inspections were conducted at two sites participating in the conduct of study Protocol EB-101-CL-301. The inspections did not reveal significant problems impacting the data submitted in support of this BLA. Table 2 below summarizes the BIMO inspections.

Table 2: Summary of BIMO Inspections of Sponsor and Clinical Investigators

Site ID	Number of Subjects Randomized	Location	483 Issued?	Final Inspection Classification
Sponsor	Not applicable	Abeona Therapeutics Inc. Cleveland, Ohio	No	No action indicated
01	10	Stanford University, School of Medicine, Redwood City, California	No	No action indicated
02	1	UMass Medical School Clinical Research Center, Worcester, MA	No	No action indicated

Source: From BIMO review

Abbreviations: BIMO, Bioresearch Monitoring Program Information

3.3 Financial Disclosures

Covered clinical study (name and/or number): EB-101-CL-301: VIITAL Study 14563/31095 EB-101: Study 14563/31095
Was a list of clinical investigators provided? X Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: 23
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 One investigator is a member of the scientific advisor board for Abeona Therapeutics. The investigator submitted the required explanation see Appendix 1.

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1

Significant payments of other sorts: 1

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes, See Appendix 1

Is a description of the steps taken to minimize potential bias provided?

☐ Yes ☒ No (Request information from applicant) Yes, see Appendix 2

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☒ No (Request explanation from applicant)

Reviewer Comment:

- Both Applicant and sub-investigators (b) (4), (b) (6) disclosed a financial arrangement. (b) (4), (b) (6) was recruited as a consultant to serve on the advisory board meeting and pre-meeting survey for which he received payment. In this role, (b) (4), (b) (6) did not participate in the design of the study, selection of endpoints, nor the statistical analysis plan. As a plastic surgeon, (b) (4), (b) (6) assisted with the application of EB-101 sheets based on instruction from the Principal Investigator, Dr. Jean Tang.
- Because (b) (4), (b) (6) is not part of the Clinical Trial Research Unit (CTRU) and therefore not responsible for collecting study data or endpoint assessments, the potential for bias is minimal.
- No significant issues with financial disclosures were identified that could lead to undue bias in the data submitted in support of this BLA. Please see Appendix for additional details.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

EB-101 is a sheet, one to three cell layers thick, with a surface area of 40 cm² (ca. 7.5 x 5.5 cm) made up of primary autologous keratinocytes transduced ex vivo with a (b) (4) (b) (4) virus derived retroviral vector (LZRSE) containing full-length human COL7A1 gene (LZRSE-COL7A1) to form gene-corrected epidermal sheets with normal C7 expression.

EB-101 is manufactured in a closed system from raw materials and reagents that meet acceptable quality standards. All assays are adequately validated, and the manufacturing process produces product of acceptable quality

After release of the EB-101 product, it is hand delivered to the appropriate health care setting for administration to the skin wounds of subjects with RDEB.

The CMC review team concluded that the manufacturing material, process, and controls can yield EB-101 with consistent quality attributes.

Please refer to Chemistry, Manufacturing, and Controls review for further details.

4.2 Assay Validation

Please refer to Chemistry, Manufacturing, and Controls review for further details.

4.3 Nonclinical Pharmacology/Toxicology

The nonclinical development program for EB-101 consisted of in vitro and in vivo components. Keratinocytes obtained from healthy human volunteers (HV) and patients with recessive dystrophic epidermolysis bullosa (RDEB) were successfully transduced by LZRSE-COL7A1 (retroviral vector; RVV) or vectors similar to the RVV. Keratinocytes from HV or patients with RDEB were transduced with the RVV or vectors similar to the RVV and expanded or grown into sheets. Transduced keratinocytes or keratinocyte sheets were affixed to a (b) (4) of human acellular dermal matrix or (b) (4) to generate nonclinical products representative of EB-101. These nonclinical products were then implanted into excisional dermal wounds generated in (b) (4) (RDEB model). The RVV or similar vectors remained confined to explanted nonclinical products at (b) (4) sacrifice. Human collagen VII (Col7) was detected in explanted nonclinical products up to 12-months post-implantation. Histological evaluation of explanted nonclinical products revealed normal epidermal differentiation, localization, and assembly of Col7. There were no gross or histopathological findings in any tissue assessed, including explanted nonclinical products. Integration site analysis was performed on RDEB keratinocytes transduced with the RVV. ISA did not indicate clonality post-transduction, and there was no evidence of RVV preference to integrate near genes associated with malignancy.

Please refer to the P/T review for further details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

EB-101 consists of a subject's own cells that have been gene-modified through retroviral transduction to express the *COL7A1* gene to produce C7 protein. The resultant cells are formed into cellular sheets for topical application onto wounds.

4.4.2 Pharmacokinetics Assessment

There were no pharmacokinetics studies performed.

4.4.3 Pharmacodynamics Assessment

In studies 14563/31095, the NC2 domain of C7 and anchoring fibrils were detected in biopsies from six patients at three months and five patients at six months. At 1-year post-treatment, three out of seven patients were positive for either NC2 or anchoring fibrils. At two years, two out of three patients with biopsies were positive for either NC2 or anchoring fibrils (one patient was positive for both anchoring fibrils and NC2; the second patient was positive only for NC2, as an additional biopsy for anchoring fibrils assessment was not obtained).

In Study EB-101-CL-301, anchoring fibrils were present in biopsy from four out of nine evaluated subjects during screening clinic visit. The post-treatment analysis at week 12 clinical visit were not completed (this was up to the discretion of the principal investigator). In 12 evaluated patients, pre-treatment biopsies from 2 patient had positive NC2 staining, and one patient had a weak positive staining result. In 10 evaluated patients, pre-treatment biopsies from 8 patients had positive NC1 staining, and one had a weak positive staining result. Out of the 5 patient biopsies collected for NC2 analysis at the week 12 post-treatment clinic visit, one biopsy had a weak positive staining result.

4.4.4 Immunogenicity Assessment

In studies 14563/31095, circulating anti-C7 antibodies were observed in two out of seven patients, which resolved without intervention by 1-year post-treatment. During LTFU, these patients did not exhibit new fevers, worsening of generalized blistering outside of grafted areas, anaphylaxis, elevated liver enzymes, or abnormal kidney function, which would be concerning for a potential systemic immune response. Tissue-bound antibodies beyond trace staining were detected in 4 patients, which resolved in three patients at 1 year follow-up. In one patient, localized immune reactants were observed at treated sites up to 2 years after treatment. Anti-C7 cytotoxic T cells were not present in evaluated blood samples, obtained at clinic visits at screening or at post-grafting follow-up visits at 4, 12, 25, 38, or 52 weeks.

In Study EB-101-CL-301, all tested patient biopsies were negative for C7 immune complexes at screening, 12, and 24 weeks. No systemic immunologic responses were reported during the study. Because of the small sample size, there is limited data to determine the effect of anti-C7 antibodies on the pharmacodynamics, safety, and efficacy.

4.4.5 Replication Competent Retrovirus (RCR) Assessment

In studies 14563/31095, no instances of positive RCR results were observed in evaluated samples, obtained at clinic visits at screening or at post-grafting follow-up visits at 4, 12, 25, 38, or 52 weeks or 2, 3, 4, or 5 years.

In study EB-101-CL-301, no instances of positive RCR results were observed at clinic visits at screening or on 6, 12, or 24 weeks.

In ongoing study EB-101-LT-001, RCR testing in blood is done for up to 5 years. No instances of positive RCR results were observed at months 6 or 18 in 6 patients.

4.5 Statistical

The Statistical reviewer agreed with the Applicant's analyses and conclusions. Please see statistical review for details.

4.6 Pharmacovigilance

There have been two ongoing studies and 1 proposed study to collect long-term safety information of EB-101 in treated patients with RDEB:

- Study EB-101-LT-001 (Study LT-001) is an ongoing long-term follow-up study in subjects who have completed Study EB-101-CL-301 or have been rolled over from Study 14563/31095. Subjects from Study EB-101-CL-301 will be followed for 15 years (5 yearly clinic visits followed by 10 yearly telephone visits) and patients from Study 14563/31095 will be followed for up to 10 years with telephone visits only.
- Study EB-101-CL-302 (Study 302) is a Phase 3b study in new and previously EB-101 treated subjects. Patients will be followed for approximately six months in this study and then followed in Study EB-101-LT-001.
- Study Pz-cel-RY-401 is a post-marketing, long-term safety follow-up registry of RDEB patients treated with the product. Patients will be followed annually for up to 15 years post-application and assessments will be conducted through remote data collection.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical program of EB-101 consists of the following studies:

- Completed studies:
 - Phase 3 study: Study EB-101-CL-301
 - Phase 1/2a study: Study 14563/31095
- Ongoing studies:
 - LTFU study: Study EB-101-LT-001
 - Phase 3b study: Study EB-101-CL-302

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The sources for this review are the clinically relevant modules in the BLA submission:

- The administrative and prescribing information in module 1
- Summary clinical information in module 2.5 and 2.7
- Clinical study reports in module 5 including the narrative clinical study reports, appendices, tabulation and analysis datasets, case report forms, and literature references submitted by the Applicant.

5.3 Table of Studies/Clinical Trials

Table 3: Summary of Clinical Studies

Study Name/ Status	Patient Population	Study Design	Number of Patients/ Wounds Treated
14563 EB-101/ Completed	13 years or older, genetic testing (b) (4) confirming COL7A1 mutations, positive expression NC1+ in the skin	Phase 1/2a single-center study to evaluate the safety and efficacy of one-time surgical application of 6 EB-101 sheets for 52 weeks in the treatment of patients aged 13 and older with RDEB	7 patients were treated with EB-101 (5 male and 2 female). 42 grafted wounds: 38 chronic treated, 4 induced treated, 6 control wounds
31095 LTFU EB-101/ Completed	Patients previously followed for 52 weeks in Study 14563 EB-101 who underwent surgical application of EB-101	Single-center, LTFU to Study 14563 EB-101 in which patients treated with EB-101 were followed with annual in-clinic visits for at least 5 years and then with annual telephone contact for the patient's lifetime. Subsequently, patients rolled over into Study EB-101-LT-001, and Study 31095 LTFU EB-101 was therefore completed. Patient participation in Study 31095 LTFU EB-101 ranged from 4 to 8 years prior to the start of Study EB-101-LT-001.	All 7 patients from Study 14563 EB-101 were enrolled. 5 patients completed the study.
EB-101-CL-301/Completed	6 years or older, clinical diagnosis of RDEB, must have at least 2 matched eligible wound sites (1 pair)	Phase 3 multicenter, randomized, intra-patient-controlled study comparing one-time surgical application of ≤6 EB-101 sheets to standard of care treatment. The duration of follow-up was 6 months posttreatment with EB-101.	11 patients were treated with EB-101 (4 male and 7 female) 43 randomized treated wounds, 24 randomized control wounds, 14 non-randomized treated wounds
EB-101-LT-001/ Ongoing	6 years or older, prior study treatment with EB-101	Multicenter, open-label, long-term follow-up (LTFU) study. Patients from Study EB-101-CL-301 are followed for 15 years after treatment with EB-101, and patients from Study 31095 LTFU EB-101 are followed via yearly telephonic visits to ensure at least 10 years of post-clinic visit follow-up.	As of data cutoff date for this safety update, 16 patients from previous studies with EB-101 were enrolled (8 females and males).

Source: The reviewer adapted from the clinical study overview Table 1 of the 120-day Safety Update Report page 6, submitted BLA 125807/0.

Abbreviations: LTFU, long-term follow-up; NC1+, non-collagenous region 1 of the type VII collagen molecule; RDEB, recessive dystrophic epidermolysis bullosa.

5.4 Consultations

5.4.1 Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

Not applicable

5.5 Literature Reviewed

This review team consulted FDA regulatory guidance documents and published, peer-reviewed literature for background and context regarding the targeted disease and the MOA of the product.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: EB-101-CL-301 (VIITAL, Study 301)

Study Title: A Phase 3 efficacy and safety study of Prademagene Zamikaracel (EB-101) for the treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB).

Clinical Trial Registry Identifiers: ClinicalTrials.gov: NCT04227106

6.1.1 Objectives

The primary objective was to evaluate the efficacy and safety of EB-101 for the treatment of RDEB subjects with large, chronic wounds.

Reviewer Comment:

- *While EB-101-CL-301 was the pivotal study with a primary and secondary focus to demonstrate efficacy of EB-101 in treating RDEB wounds, assessing safety was a stated objective although no prespecified safety endpoints were proposed.*

6.1.2 Design Overview

This is a multicenter, randomized, intra-subject controlled, phase 3 study comparing surgical application of EB-101 with SOC for the treatment of large, chronic wounds in patients with RDEB. Within each subject, matched wound pairs were randomized in a 1:1 ratio of EB-101 versus SOC. The matched wounds needed to be clean with pink granulation tissues without drainage, have a reasonable distance away from each other, have an area $\geq 20\text{cm}^2$, present for ≥ 6 months and be classified as a stage 2 wound which was defined as an open skin wound with partial thickness loss of dermis that has not extended through the dermis into the subcutaneous tissue. Wounds on active joints that cannot be adequately and safely immobilized, points of significant pressure (for example: bottom of foot, tip of elbow) face, and areas close to mucous membranes (for example: genitourinary, oral and anal mucosa) were excluded. Wounds pairs on anterior

trunk and on opposing limbs were preferred. For each patient, suitable wound pairs were identified for randomization and treatment. The maximum wound pairs in any one patient were 5. Each pair of wounds was assigned either treatment with EB-101 or with standard of care (SOC). The follow-up period was from Day 14 to Week 24 + 2 Weeks with direct investigator assessment of randomized wound pairs and any additional EB-101 treated wounds. Direct investigator assessed wound healing through direct visual inspection by the Principal Investigator or designee who is a trained dermatologist experienced in EB. The primary endpoints were assessed at Week 24 (Month 6) and confirmed at Week 26. The secondary endpoints were assessed at Week 12 (Month 3) and Week 24 (Month 6).

Following completion of the study, subjects were enrolled in a Long-Term Follow-Up study of 15 years duration, with in-clinic monitoring performed yearly for 5 years, followed by annual phone/questionnaire follow-up thereafter for 10 years.

Reviewer Comment:

The study design had its strengths and limitations:

- 1. Strength: Each subject serving as their own control minimized potential inter-subject variability in disease progression and assessments during the study follow up.*
- 2. Limitation: The lack of blinding of the wound sites and assessors raised concerns for potential assessor's bias in evaluating EB-101 treated wounds versus control wounds. Blinding would be difficult to achieve due to the surgical application of EB-101 compared to SOC treatment (control). To reduce this potential bias, wound healing assessed by photographic comparison was deemed acceptable.*
- 3. Limitation: Given the intra-subject-controlled design, and the randomization scheme applied, there is a possibility for mismatched wounds. Furthermore, the open-label design lends itself to potential selection bias with respect to the wound(s) selected for treatment in the study.*

6.1.3 Population

Key eligibility criteria for inclusion in the study were: 6 years of age or older, clinical diagnosis of RDEB and at least two matched eligible wound sites present for ≥ 6 months and with an area $\geq 20\text{cm}^2$. The key exclusions are evidence of immune response to C7 by indirect immunofluorescence (IIF) or enzyme-linked immunoassay (ELISA), evidence or history of squamous cell carcinoma (SCC) and hypersensitivity to vancomycin or amikacin.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each subject received up to approximately six 40 cm^2 EB-101 sheets. Two to 6 of the 40 cm^2 sheets were used in a single treatment session. The maximum estimated treatment surface area for all the EB-101 sites were approximately 240 cm^2 .

6.1.5 Treatment Procedure/Product Application

A plastic surgeon and an anesthesiologist experienced in treating RDEB patients apply EB-101 affixed with staples and suture after all wounds were cleansed and debrided. Topical antibiotics was applied, and wound was covered with non-adhesive and absorbent foam dressing. At the discretion of the plastic surgeon and Principal Investigator, splints were used to immobilize the treated areas to prevent any trauma to EB-101.

6.1.6 Sites and Centers

Table 4: List of Investigators and Study Sites

Site #	Principal Investigator/Site Address	Number of subjects enrolled
01	Jean Yuh Tang, M.D Ph.D Stanford Medicine Outpatient Center Redwood City, CA	10
02	Karen Wiss, M.D University of Massachusetts UMass Memorial Health Care Worcester, MA	1

6.1.7 Surveillance/Monitoring

Schedule of Assessment:

The schedule of assessment was categorized into 3 phases: screening, Day 0 and follow-up visits. The interval of the follow-up visits ranging from weekly, bi-weekly, tri-weekly to a maximum interval of 6 weeks.

Screening Phase: The following procedures were conducted or reviewed: informed consent, randomization of eligible wounds, eligibility criteria, medical history, concomitant medications, adverse events, demographics, physical examination, echocardiogram, electrocardiogram, anesthesiology/plastic surgeon consult, EB-101 manufacture, digital photograph with ruler and quality of life in Epidermolysis Bullosa (EB-QOL).

Day 0: Inpatient admission, EB-101 treatment and review of vital signs, medical history, concomitant medications, and adverse events,

Follow-up Visits: routine review of vital signs, adverse events, concomitant medications, physical and skin examination, and digital photographs. Recurring assessment of safety laboratory tests, pathology testing of skin biopsy via DIF, and direct assessment of randomized and non-randomized wounds treated with EB-101. Recurring outcome measures assessed were Patient-Reported Outcomes Measurement Information System (PROMIS)-Pediatric pain quality sensory short form, Patient-Reported Outcomes Measurement Information System (PROMIS)-Pediatric pain quality affective short form, Worst Itch-Numeric Rating Scale (WI-NRS), Zarit Burden Interview (ZBI)-12, pain severity scale via Wong-Baker FACES, and Patient Global Impression of Change (PGI-C) for blistering.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

There were two co-primary endpoints in the study (randomized treated versus control wounds):

- The proportion of randomized wound pairs with $\geq 50\%$ healing from Baseline at Week 24 (Month 6) as determined by the Principal Investigator [to be confirmed at Week 26]
- Pain reduction assessed by the mean differences in scores of the Wong-Baker FACES scale [or numeric rating scale (NRS)] between randomized wound pairs at Week 24 (Month 6)

Secondary Endpoint:

The proportion of randomized wound pairs with complete wound healing (i.e., re-epithelialization with no drainage or erosion and presence of only minor crusting) from Baseline at Week 12 and Week 24 as determined by direct assessment by the Principal Investigator

Reviewer's Comment:

- *The clinical endpoints are relevant, clinically meaningful, and measurable over the study's duration.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Methods:

The intention-to-treat (ITT) population, which consisted of all randomized wound pairs (i.e., EB-101 treated and SOC control) treated on Day 0 were the primary analysis population for efficacy.

Subgroups Analysis:

A subgroup analysis was performed for each of the co-primary endpoints based on wound location. Analysis methods were identical to the primary analyses, for each primary endpoint respectively, but where each wound pair was stratified according to wound location, defined as posterior trunk wounds versus all other locations.

Missing Data:

The last observation carried forward (LOCF) method was the primary method for dealing with missing data for the primary and secondary endpoint analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The ITT population included all 11 subjects whose primary wounds were randomized.

6.1.10.1.1 Demographics and Baseline Characteristics of the Enrolled Population

Demographic characteristics for the ITT/safety population are summarized in Table 5.

Table 5: Demographic and Baseline Characteristics

Characteristics	Overall (N=11)
Age at RDEB Diagnosis (months)	-
n	11
Mean (SD)	63.9 (123.14)
Median (Min, Max)	0.0 (0, 372)
Age (years)	-
Mean (SD)	22.5 (9.10)
Median (Min, Max)	21.0 (6, 40)
Sex, n (%)	-
Male	4 (36.4)
Female	7 (63.6)
Race, n (%)	-
White	10 (90.9)
Other (Unknown)	1 (9.1)
Ethnicity, n (%)	-
Hispanic or Latino	2 (18.2)
Not Hispanic or Latino	8 (72.7)
Unknown	0 (0.0)
Not Reported	1 (9.1)
Height (cm)	-
Mean (SD)	159.01 (21.719)
Median	164.00 (101.6, 182.7)
Weight (kg)	-
Mean (SD)	48.27 (18.393)
Median (Min, Max)	48.20 (12.1, 75.6)
BMI (kg/m ²)	-
Mean (SD)	18.64 (6.387)
Median (Min, Max)	16.90 (10.4, 33.4)
Number of Wounds per patient	-
Mean (SD)	9.1 (1.64)
Median (Min, Max)	10.0 (6, 11)

Source: Reviewer adapted from BLA 125807 CSR Page 64

Notes: The safety analysis population consists of all patients with ≥1 wound that has been treated with EB-101. Number of wounds includes randomized treated, randomized control and non-randomized treated wounds.

Abbreviation: BMI, body mass index; RDEB, recessive dystrophic epidermolysis bullosa; SD, standard deviation.

The extent of exposure for the randomized wounds are summarized in Table 6 below.

Table 6: Extent of Wound Exposure

Parameter	Randomized Treated (N=43)	Randomized Control (N=43)
Number of wounds	-	-
n ^a	11	11
Mean (SD)	3.9 (1.04)	3.9 (1.04)
Median (Min, Max)	4 (2, 5)	4 (2, 5)
Total body surface area	-	-
Covered by EB-101 (cm ²)	-	-
n ^a	11	-
Mean (SD)	156.4 (41.78)	-
Median (Min, Max)	160 (80, 200)	-
Total body surface area	-	-
Treated (%) ^b	-	-
n ^a	11	-
Mean (SD)	1.111 (0.2238)	-
Median (Min, Max)	1.150 (0.67, 1.37)	-
Wound duration (months)	-	-
n ^c	43	43
Mean (SD)	74.2 (88.44)	76 (80.71)
Median (Min, Max)	60 (6, 252)	60 (6, 252)

Source: Reviewer adapted table from BLA 125807/0; CSR EB-101-CL-001, page 96

^a Number of patients with wounds in each category.

^b Total body surface area covered in control wounds was not collected.

^c Number of wounds in each category

Abbreviations: SD, standard deviation

6.1.10.1.2 Subject Disposition

A total of 15 subjects signed consent and entered the screening period of the study. There were 4 screen failures. Eleven subjects were randomized and received treatment. All randomized patients (100%, n=11) completed the study. EB-101 was applied onto 43 randomized wounds in 11 patients treated in the study; 43 randomized, paired control wounds were treated with SOC control treatments.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints.

Among randomized wounds in the intent-to treat (ITT) population, a statistically significantly higher proportion of EB-101 treated wounds (81.4%) were reported to have healed ≥50% from Baseline compared with that of control wounds (16.3%; $P < 0.0001$) at Week 24 (Table 7) as determined by direct assessment of the Principal Investigator.

Table 7: Proportion of Randomized Wound Pairs With $\geq 50\%$ Healing from Baseline at Week 24

	Treated (N=43)	Control (N=43)	
$\geq 50\%$ Healing from Baseline at Week 24 ^b n1/n2 (%) ^a	35/43 (81.4%)	7/43 (16.3%)	-
Test Statistic ^c 2-Sided P Value ^d			0.67 <0.001

Source: Reviewer adapted from EB-101-CL-001 CSR page 68-69

Complete wound healing is defined as re-epithelialization with no drainage or erosion and presence of only minor crusting. If the extent of healing is $\geq 75\%$ of Baseline, complete wound closure was assessed.

^a n1 = Number of wounds in category for healing improvement percentage from baseline; n2 = Total number of wounds with non-missing healing improvement category.

^b The proportion of wounds achieving a healing category at Week 24 must be confirmed at least 2 weeks later to be coded as 1; otherwise, it was coded as 0.

^c The test statistic is calculated as follows: Wound sites achieving $\geq 50\%$ healing at the target analysis time were recorded as 1 and otherwise as 0. Healing rates for the treated and control wounds and the difference between them were calculated in a 2x2 table. For each randomization pair, the difference between treated and control wound sites was calculated first. The difference was averaged across all matched pairs within a participant. The participant-level average rates were averaged across all study participants.

^d 2-Sided P value is derived using a randomization test (also known as a permutation test within matched pairs).

Among randomized wounds in the ITT population, mean pain severity reduction from baseline at Week 24 was statistically significantly greater in the EB-101 treated wounds (3.07) than in the control wounds (0.90; $P=0.0002$) with a mean (95% confidence interval) pairwise difference across wound pairs (n=42) of 2.14 (1.07, 3.21) as illustrated in Table 8:

Table 8: Pain Reduction Assessed by Wong-Baker FACES Scale (or NRS)

	Treated Wounds (N=43)	Control Wounds (N=43)	Randomized Wound Pairs (N=42)^a
Baseline	-	-	-
n	43	42 ^a	-
Mean (SD)	5.12 (3.126)	4.38 (3.036)	-
95% CI of mean	(4.15, 6.08)	(3.43, 5.33)	-
SE	0.477	0.468	-
Median (Min, Max)	4 (0, 10)	4 (0, 10)	-
Pain reduction at week 24	-	-	-
n	43	42	-
Mean (SD)	3.07 (3.188)	0.90 (2.730)	-
95% CI of mean	(2.09, 4.05)	(0.05, 1.76)	-
SE	0.486	0.421	-
Median (min, max)	2 (-2, 10)	0 (-8, 6)	-
Test Statistic ^b 2-Sided P Value			2.23 0.0002

Source: Reviewer adapted from CSR EB-101-CL-001 page 74-75

Notes: Intention-to-treat population consists of all randomized wound pairs that are treated on day 0. Missing data is imputed using the Last Observation Carried Forward method. Imputation was done at Week 24 for randomized wounds only. Pain was assessed primarily via the Wong-Baker FACES pain rating scale or Numeric Rating Scale (NRS) (Wong-Baker FACES was not available prior to Protocol Version 6).

^a Only 42 subjects with documented baseline.

^b The test statistic is calculated as follows: For the target analysis time, the pain reduction is calculated for each wound. A positive value represents a pain reduction, and a negative value represents pain worsening. The pair differences in pain

reduction were calculated as randomized treated wound – randomized control wound for each matched pair first and averaged across all pairs within a participant. The participant-level average values were then averaged across all study participants

Abbreviations: CI, confidence interval; SD, standard deviation.

Reviewer Comment:

- *All wound pairs were assessed throughout the study by direct visual examination of the wound pairs by the Principal Investigator using his or her clinical expertise to determine the extent of wound healing. Given the lack of blinding, evaluation of efficacy was subject to potential bias. However, given that the trial was randomized, this bias is expected to occur equally/similarly in the two groups.*
- *The photographic images for the randomized wound pairs do not effectively delineate control and treated wounds, especially for wounds located within the same anatomical region. The protocol described small (~1 mm) tattoo dots placed at the corners of EB-101 and the edges of control wound areas. But not all photographic images of the randomized wound pairs clearly distinguish the randomized EB-101 wounds from the controls. This may have made assessment of wound healing difficult or imprecise, but randomization is expected to reduce this bias making this risk similar across both groups.*
- *Some wounds demonstrated transient worsening prior to Week 24+2-week endpoint assessment period, making it difficult to effectively assign improvement to EB-101. Perhaps the re-opening prior to the Week 24-2-week period, indicated lack of effect, and later improvements would have naturally occurred. This is difficult to incorporate into the efficacy assessment but randomization and use of an inpatient control strategy likely minimized the potential for this bias in the assessments and analyses of the efficacy endpoints.*

6.1.11.2 Analyses of Secondary Endpoints

Among randomized wounds in the ITT population, a statistically significantly higher proportion of EB-101 treated wounds (Week 12: 14%, $P=0.0316$; Week 24: 16.3%, $P=0.0160$) were reported to have completely healed at Weeks 12 and 24 from Baseline compared with (0%) of control wounds at both time points (Table 9) as determined by direct assessment of Principal Investigator.

Table 9: Proportion of Randomized Wound Pairs with Complete Healing at Week 12 and 24

	Treated (N=43)	Control (N=43)	Randomized Wound Pairs (N=43)
Proportion of wounds with healing improvement from baseline n1/n2 (%) ^a Week 12 Complete Wound Healing from Baseline Confirmed	6/43 (14.0)	0/43 (0)	-
Mean difference in healing rates between treated and control wounds across all study participants ^c 2-Sided P Value	-	-	0.19 0.0316
Week 24 Clinic Visit Complete Wound Healing from Baseline Confirmed ^b	7/43 (16.3)	0/43 (0)	-
Test Statistic: Mean difference in healing rates between treated and control wounds across all study participants ^c 2-Sided P Value	-	-	0.13 <0.0160

Source: Reviewer adapted from CSR EB-101-CL-001. Pages 80-81

Notes: Intention-to-treat (ITT) population consists of all randomized wound pairs that are treated on day 0. Missing data is imputed using the Last Observation Carried Forward (LOCF) method. Imputation was done at Weeks 12 and 24 for randomized wounds only.

Complete wound healing is defined as re-epithelialization with no drainage or erosion and presence of only minor crusting.
^an1 = Number of wounds in category for healing improvement percentage from baseline; n2 = Total number of wounds with non-missing healing improvement category.

^bThe proportion of wounds achieving a healing category at Week 24 must be confirmed at least 2 weeks later to be coded as 1; otherwise, it was coded as 0.

^c Wound sites with complete healing at the target analysis time were recorded as 1 and otherwise as 0. Healing rates for the treated and control wounds and the difference between them were calculated in a 2x2 table. For each randomization pair, the difference between treated and control wound sites was calculated first. The difference was then averaged across all matched pairs within a participant. The participant-level average rates were then averaged across all study participants.

6.1.11.3 Analyses of Exploratory Efficacy Endpoints

The exploratory analysis explored a wide array of endpoints ranging from investigator assessments, patient-reported and caregiver reported outcomes. These includes: changes from baseline in wound healing ($\geq 75\%$), pain reduction measured by Wong-Baker FACES scale, Caregiver Global Impression of Pain (CrGI pain), caregiver Zarit Burden Interview Short Form (ZBI-12), frequency of related AEs and SAEs, itch severity measured by Worse Itch via numeric rating scale (NRS), wound site improvement by Patient Global Impression of Change (PGI-C), blistering assessment by PGI-C-Blistering score, and pain quality and interference measured by Pediatric Short Form 8a version of pain Quality (PROMIS) and pain interference scales respectively.

Table 10 highlights the proportion of randomized wounds in the ITT population with $\geq 75\%$ healing from Baseline were statistically significantly higher in the EB-101 treated wounds compared with that of control wounds at Week 12 (treated wounds: 46.5%; control wounds: 7.0%; $P=0.0001$) and Week 24 (treated wounds: 65.1%; control wounds: 7.0%; $P< 0.0001$). Overall, results for the exploratory endpoints were supportive of the primary and secondary endpoints and demonstrated beneficial treatment effect with EB-101 treatment.

Table 10: Proportion of Randomized Wound Pairs with $\geq 75\%$ Healing from Baseline at Week 12, and Week 24

Visit	Randomized Treated (N=43)	Randomized Control (N=43)	Randomized Wound Pairs (N=43)
Week 12 Clinic Visit	-	-	-
$\geq 75\%$ Healing from Baseline	20/43 (46.5)	3/43 (7)	-
Test Statistic: Average difference in healing rates between treated and control wounds across all study participants ^c 2-Sided <i>P</i> Value ^d	-	-	0.39 <0.0001
Week 24 Clinic Visit	-	-	-
$\geq 75\%$ Healing from Baseline	28/43 (65.1)	3/43 (7)	-
Test Statistic: Average difference in healing rates between treated and control wounds across all study participants ^c 2-Sided <i>P</i> Value ^d	-	-	0.58 <0.0001

Source: Reviewer adapted from CSR EB-101-CL-001. Pages 83-84

Notes: Intention-to-treat population consists of all randomized wound pairs that are treated on day 0. Missing data is imputed using the Last Observation Carried Forward method. Imputation was done at Weeks 12 and 24 for randomized wounds only. Complete wound healing is defined as re-epithelialization with no drainage or erosion and presence of only minor crusting. If the extent of healing is $\geq 75\%$ of Baseline, complete wound closure was assessed.

^c The test statistic is calculated as follows: Wound sites achieving $\geq 75\%$ healing at the target analysis time were recorded as 1 and otherwise as 0. Healing rates for the treated and control wounds and the difference between them were calculated in a 2x2 table. For each randomization pair, the difference between treated and control wound sites was calculated first. The difference was averaged across all matched pairs within a participant. The participant-level average rates were averaged across all study participants.

^d 2-Sided *P* value is derived using a randomization test (also known as a permutation test within matched pairs),

6.1.11.3 Subpopulation Analyses

A subgroup analysis was performed for each of the co-primary endpoints based on wound location. Analysis methods were identical to the primary analyses, for each primary endpoint respectively, but each wound pair was stratified according to wound location defined as posterior trunk wounds versus all other locations. The results were similar to the overall results.

6.1.11.4 Dropouts and/or Discontinuations

Please refer to [Section 6.1.10.1.3](#)

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses were planned without formal statistical inferences. However, analyses were conducted including *P* values in an exploratory manner.

Additional efficacy analyses for pain reduction were performed to evaluate the treatment effect of EB-101 in patients with wounds with ≥ 6 pain severity at baseline. Further, efficacy analyses presented at Week 6 were also not planned but were conducted.

Overall efficacy summary

In summary, EB-101 demonstrated efficacy based on the co-primary efficacy endpoints of the difference in the proportion of $\geq 50\%$ healing from Baseline at Week 24 (confirmed at Week 26 by the PI) and mean differences in pain reduction based on the Wong-Baker FACES scores at Week 24 (Month 6) between the randomized wounds pairs.

For the EB-101 treated wounds, 79.1% and 81.4% achieved $\geq 50\%$ healing from Baseline at Weeks 12 and 24, respectively, compared to 18.6% and 16.3% ($P < 0.0001$) in the control group. Of the 43 randomized EB-101 treated wounds, only 8 wounds were not categorized as achieving $\geq 50\%$ wound healing by Week 24. Wounds treated with EB-101 had a mean pain reduction of 3.07 points on the validated Wong-Baker FACES Scale after 24 weeks, compared to 0.90 in the control group ($P = 0.0002$).

Efficacy was further supported by the secondary endpoint of proportion of randomized wounds with complete wound healing from Baseline at Week 12 and Week 24 which demonstrated statistically significant improvement in healing of wounds treated with EB-101 compared to SOC in the ITT population (Week 12: 14.0%, $P = 0.0316$; Week 24: 16.3%, $P = 0.0160$). Additionally, a higher proportion of EB-101-treated wounds were reported to have completely healed at Week 6 compared with control wounds (EB-101: 7.1%, control: NA; $P = 0.4997$). Additionally, 46.5% and 65.1% of treated wounds achieved $\geq 75\%$ healing from Baseline at Weeks 12 and 24, respectively, compared to 7.0% and 7.0% ($P < 0.0001$) in the control group.

6.1.12 Safety Analyses

The safety analysis (SA) population consisted of all patients with ≥ 1 wound treated with EB-101.

6.1.12.1 Methods

Safety analyses were performed using the Safety Population. There was a total of 100 wounds from 11 subjects assessed for safety. Eighty-three (83) wounds were randomized to either EB-101 treated or control wounds. There were 14 non-randomized wounds. Adverse events (AEs) were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

6.1.12.2 Overview of Adverse Events

The mean number of wounds was 3.9 (1.04) for both treated and control groups among randomized wounds. The mean total body surface area treated by EB-101 was 156.4 (41.78) cm² among randomized (Table 11).

Table 11: Summary of Exposure to EB-101

Total Exposure Time (months)	Randomized Wound Treated: (N=43)	Randomized wound Control: (N=43)
Number of wounds	-	-
n ^a	11	11
Mean (SD)	3.9 (1.04)	3.9 (1.04)
Median	4.0	4.0
Min, Max	2, 5	2, 5
Total BSA Covered by EB-101 (cm2)	-	-
n ^a	11	-
Mean (SD)	156.4 (41.78)	-
Median	160.0	-
Min, Max	80, 200	-
Wound Duration (months)	-	-
n ^b	43	43
Mean (SD)	74.2 (83.44)	76 (80.71)
Median	60	60
Min, Max	6, 252	6, 252

Source: Reviewer adapted table 23 from EB-101-CL-301 CSR page: 96.

Total body surface area covered by EB-101 = 40 cm² * number of treated wounds. Body Surface Area is derived using Mosteller formula (Body Surface Area (m2) =sqrt((height(cm) * weight (kg))/3600))

^aNumber of patients with wounds in each category.

^bNumber of wounds in each category.

Abbreviation: SD, standard deviation; BSA, Body surface area

Summary of Adverse Events

A total of 62 TEAEs were reported in 11 (100%) patients (Table 12). There were no deaths in this study. There were 5 serious adverse events (SAEs) in 2 subjects (18.2%) which ranged from moderate to severe. There were 4 TEAEs in 4 subjects (36.4%) which were assessed as related to EB-101.

Table 12: Summary of TEAEs

Category	Overall (n=11)
All TEAEs	-
Number of subjects (%)	11 (100%)
Number of Events	62
Serious TEAEs	-
Number of subjects (%)	2 (18.2%)
Number of Events	5
TEAEs related to EB-101	-
Number of subjects (%)	4(3.6) ^a
Number of Events	4

Source: Reviewer adapted table from EB-101-CL-301 CSR Table 24 page: 98

Notes: The safety analysis population consists of all patients with ≥1 wound that has been treated with EB-101.

TEAEs are defined as any AE with an onset on or after the date of EB-101 application. Study wound AEs are not included in this table and are summarized separately.

^a Possible, Probable, and Definitely Related are considered Related to EB-101, a missing relationship will conservatively be considered Related to EB-101 as well.

Abbreviations: AEs, adverse events; TEAE, treatment-emergent adverse event

TEWAEs

Among randomized wounds, there were 24 and 7 treatment-emergent wound adverse events (TEWAEs) reported in treated and control wounds respectively (Table 13). Within the non-randomized treated wounds, 11 TEWAEs occurred in 3 subjects. There were no serious TEWAEs. There were 3 TEWAEs events each attributed to EB-101 in both the randomized treated wounds and control wounds. These TEWAEs occurred in 1 subject each in the randomized treated and control subjects. Three TEWAEs occurred in the non-randomized wounds in 1 subject. All related TEWAEs were for procedural pain.

- TEWAEs each in treated and control wounds were related to EB-101. All related TEWAEs were the PT procedural pain; and
- 15 and 4 TEWAEs in treated and control wounds, respectively, were infections.

TEWAEs reported in randomized treated and control wounds. Among non-randomized wounds, 11 events were reported. Of these,

- TEWAEs were related to EB-101. All related TEWAEs were the PT procedural pain; and
- 6 TEWAEs were infections.

Table 13: Treatment-Emergent Wound Adverse Events by System Organ Class

	Randomized Wounds		Non-randomized Wounds
-	Treated (N=43)	Control (N=43)	Treated (N=14)
Preferred Term	Wounds n (%)	Wounds n (%)	Wounds n (%)
Any TEWAE	16 (37.2) in 7 subjects	7 (16.3) in 4 subjects	(42.9) in 3 subjects
Number of events	24	7	11
Wound infection	10(23.3) in 5 subjects	4 (9.3) in 3 subjects	2 (14.3) in 1 subject
Number of events	14	4	6
Fungal infection	1(2.3) in 1 subject	0 (0.0) in 0 subjects	0 (0.0) in 0 subjects
Number of events	14	0	0
Procedural pain	(14.0) in 2 subjects	3 (7.0) in 1 subject	4 (28.6) in 2 subjects
Number of events	6	3	4
Pruritus	3 (7.0) in 1 subject	0 in 0 subjects	1 (7.1) in 1 subject
Number of events	3	0	1

Source: Reviewer adapted table from EB-101-CL-301 CSR Table 27 page: 104-105

Abbreviations: AE = adverse event; TEWAE = treatment-emergent wound adverse event.

Notes: The safety analysis population consists of all patients with ≥1 wound that has been treated with EB-101.

Treatment-emergent wound AEs are defined as any wound adverse event with an onset on or after the date of EB-101 application. TEWAEs are sorted by descending frequency of system organ class and PT. AEs with the same frequency are sorted alphabetically.

TEAE: The most frequently reported treatment emergent adverse events which was organized by system organ class and preferred term. The reported events represented $\geq 20\%$ of subjects:

- 13 TEAEs of wound infection in 6 (54.5%) subjects,
- 4 TEAEs of procedural pain in 4 (36.4%) subjects, and
- 4 TEAEs of constipation in 3 (27.3%) subjects

All 11 subjects experienced at least one TEAE event. Based on organ class, subjects experienced the following: 72.7% (8) subjects experienced 26 events of wound infections/infestations, 63.6% (7) subjects experienced 12 events of gastrointestinal disorder, 54.5% (6) subjects experienced 6 events of injury, poisoning and procedural complications, 28.3% (3) subjects had 3 events of musculoskeletal and connective tissue disorders, 18.2% (2) subjects each had 2 events each of metabolisms and nutrition disorders, psychiatric disorders and respiratory, thoracic and mediastinal disorders. 9.1% (1) subject each experienced pyrexia, drug sensitivity, leukocytosis, toe amputation and squamous cell carcinoma.

6.1.12.3 Deaths

There are no deaths in this study

6.1.12.4 Non-fatal Serious Adverse Events

Two subjects experienced 5 SAEs. None of these SAEs were considered related to EB-101.

Subject (b) (6) Wound Infection

Subject was hospitalized for 2 episodes of Grade 3 wound infection from *Staphylococcal aureus* and a grade 3 wound infection at the surgical site of the toe amputation, all requiring intravenous antibiotics. The investigator assessed the events of wound infection as unrelated to EB-101 treatment; the event was due to disease progression.

Reviewer Comment:

- *The reviewer agrees with the investigator's assessment. Wound infection is a common complication of RDEB wounds and following skin grafting.*

Subject (b) (6) Toe amputation:

On Study Day 204, she underwent Grade 3 left toe amputation due to a non-healing ulcer without osteomyelitis. The investigator assessed the SAE event, toe amputation, as due to disease progression, thus unrelated to EB-101 treatment.

Review Comment:

- *The reviewer agrees with the investigator's assessment. The subject has a history of osteomyelitis and wound dehiscence of the left great toe.*

Subject (b) (6) SCC:

24-year-old female who received EB-101 on (b) (6). Her medical history was significant for SCC of the right upper extremity (4th finger) resulting in amputation in September 2021. On Study Day 173 she presented with lesion on dorsal surface of the right hand. The lesion was biopsied with a resultant diagnosis of Grade 3 SCC. The lesion was excised with clear margins and an autologous skin graft was applied. Proviral genome testing was reported as negative. She did not receive EB-101 treatment to the affected hand. The closest area of treatment was the right mid-dorsal forearm. This SCC was assessed as unrelated to EB-101. The investigator assessed the event of SCC as due to disease progression.

Reviewer Comment:

- *The reviewer agrees with the investigator's assessment. The dorsum of the right hand was not treated with EB-101 and the proviral DNA testing of the excised lesion was reported as negative.*

6.1.12.6 Clinical Test Results

There were no clinically meaningful changes associated with treatment were observed in the vital signs or physical examination findings. However, changes in the clinical laboratory data (hematology and serum chemistry) were evident in many subjects during the study period. These changes include, but not limited to, leukocytosis, neutrophilia, anemia, thrombocytosis, elevated inflammatory markers (C-reactive protein), etc. These laboratory data suggest ongoing/background inflammation in these subjects.

Reviewer Comment:

- *The presence of pre-treatment derangement in laboratory data suggest the underlying disease may be the reason for persisting derangement post treatment, which further confounds the clinical course.*

In summary, the safety population includes all 11 subjects and the most frequent adverse reactions (incidence >5%) were wound infection, procedural pain and constipation. Two subjects experienced 5 SAEs, which were considered not related to EB-101. There were no deaths in the Phase 3 study.

6.1.13 Study Summary and Conclusions

EB-101-CL-301 was an adequately and well controlled, multicenter, randomized, intra-patient-controlled Phase 3 study of EB-101 in RDEB wounds.

The study met both its primary and key secondary endpoints and the overall safety profile for EB-101 in this study was reassuring.

6.2 Trial #2

Study Title: A Phase 1/2a single center trial of gene transfer for RDEB using LZRE-COL7A1 engineered autologous epidermal sheets (LEAES), and long-term follow-up for RDEB participants treated with LEAES.

6.2.1 Objectives

Primary: Safety

6.2.2 Design Overview

Phase 1/2a, single-center, open-label, proof-of-concept study to evaluate the efficacy and safety of EB-101 in the treatment of subjects aged 13 years and older with RDEB. This study consisted of 3 parts: 52-week study primary endpoint assessment, a 5-year long-term yearly in-clinic monitoring, and a 10-year annual phone/questionnaire follow-up.

After screening, cells are obtained and cultured for gene transfer. The target wound areas were identified and examined. The investigator induced a blister by firmly rubbing

a 40-50cm² area of skin on the anterior or lateral torso of upper or lower extremity. The subjects were enrolled and EB-101 was surgically applied by the plastic surgeon.

6.2.3 Population

The key eligibility criteria for inclusion into study (31095) were, subjects must be 13 years of age or older, have a clinical diagnosis of RDEB with 2 confirmed RDEB C7 mutations and have at least 100 to 200 cm² areas of chronically wounded areas on the trunk and/or extremities. The key exclusions were evidence of immune response to C7 by indirect immunofluorescence (IIF) or western blot, evidence or history of squamous cell carcinoma (SCC) and hypersensitivity to vancomycin or amikacin. For enrollment in Study 31095 must have received EB-101 in Study 14563

6.2.4 Study Treatments or Agents Mandated by the Protocol

The Phase 1/2a study was an open label study. There were 2 types of wounds to be grafted: acute (optional, induced approximately 24 hours prior to grafting in the Phase 1 portion of the study and measuring 40-50cm²) and chronic wounds or scars of approximately 25-50cm². Both types of wounds received EB-101.

6.2.5 Directions for Use

The blister roof of the acute wound was removed. All wounds were gently cleansed with normal saline or povidone-iodine solution. Overhanging epidermis, hyperkeratotic skin, or fibrinous material were gently debrided with scalpel, scissors, or the timed surgery electrosurgical technique (or equivalent cauterization technique), or a combination of these. Six of the 40 to 50 cm² epithelial sheets were used in a single grafting session with a maximum total grafting surface area was 300cm². Grafts were applied to the wound beds and affixed with suture, Mepitac, and/or overlying dressing. A layer of topical antibiotics was applied with antibiotic choice determined by the grafting surgeon and EB physician.

6.2.6 Sites and Centers

Table 14 lists the names of investigators and sites for study 31095.

Table 14: Investigators and Sites:

Study Phase	Principal Investigator Name and Credentials	Site Address	Number of Patients Enrolled
1	Alfred T. Lane, MD Professor Emeritus of Dermatology and Pediatrics, Stanford University	Stanford School of Medicine Palo Alto, CA	4
1/2a	Jean Y. Tang, MD, PhD Professor of Dermatology, Stanford University	Stanford Medicine Outpatient Center Redwood City, CA	3

6.2.7 Surveillance/Monitoring

Schedule of Assessments

The schedule of assessments was categorized into phases: prescreening, screening, grafting and post grafting, and post grafting follow-up.

Prescreening phase: Phone screening of subjects, transport to study location, medical history review, digital photograph of wounds, and physical and examination were obtained. These laboratory tests were conducted: genetic testing, complete blood count (CBC), chemistry, hepatic function, infectious disease (human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C) screening, pathology testing of skin biopsy via direct immunofluorescence (DIF), indirect immunofluorescence (IIF) and electron microscopy. IIF to assess immune response, keratinocyte culture, molecular analysis, immunoelectron microscopy.

Screening phase: Review and sign informed consent, consultation with anesthesiology, pregnancy testing¹ where applicable, manufacture EB-101, review of medical history and concomitant medications, verification of inclusion and exclusion criteria and adverse events assessment. EB-101 culture was obtained periodically, creation of an acute wound (to be used as control wound) and electrocardiogram/echocardiogram were conducted during this phase.

Laboratory tests: Complete blood count (CBC), chemistry, hepatic function test and replication-competent retrovirus. Pathology testing of skin biopsy via DIF, IIF and electron microscopy. IIF to assess immune response, immunofluorescence (IF) for Type VII collagen, keratinocyte culture, molecular analysis and immunoelectron microscopy.

Grafting and post grafting observation phase: Subjects received EB-101 grafting with periodic graft assessment. Subjectst were monitored inpatient for 5-7 days post grafting. Laboratory assessments conducted were CBC, chemistry, and hepatic function. Routine review of adverse events and concomitant medications. Physical and skin examination, and digital photographs were conducted periodically.

Post-grafting follow-up phase: Routine review of adverse events and concomitant medications. Physical and skin examination and digital photographs were conducted periodically. Routine assessment of laboratory tests, graft assessment, IIF for immune response, cytotoxic T cell assay, RCR evaluation, IF for Type VII collagen, molecular analysis, and pathology assessments.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of RDEB wound sites with healing $\geq 50\%$ from Baseline in treated intra-patient wound sites as assessed by Investigator's Global Assessment (IGA) at Months 3, 6, and 12. The Phase 1/2a study was initially conducted as a Phase 1 study, and the primary outcome measures were presence of C7 and anchoring fibrils and the frequency of AEs. Four (4) subjects were treated in the Phase 1 portion. After the Phase 2a portion of the study was added in 2016, the primary outcome measures were updated to include assessments of wound healing including percentage surface area of wound healing and Investigator's assessment of the graft in addition to using the Canfield system.

Secondary Efficacy Endpoints:

At months 3, 6, and 12 and annually during LTFU study the following assessments were made:

- Healed wound size for treated wounds estimated using lower range of Investigator's Global Assessment scores from Baseline at each study visit, and
- Molecular correction of C7 as assessed by:
 - Immunofluorescence (IF): The NC2 domain of C7 assessed using the LH24 antibody, and
 - Presence of AFs assessed by immunoelectron microscopy.

Safety Endpoint:

The Safety Population from both Phase 1/2a and LTFU were assessed for:

- Incidence of AEs associated with graft such as: presence of replication-competent retrovirus (RCR) in the blood, cancer, autoimmune and alloimmune reaction,
- Clinically significant changes in laboratory data such as: immune response against C7, cytotoxic T cell assay (optional at Week 52), RCR, SCC, increased blistering outside of treated areas, complete blood count with differential, metabolic panel, and bilirubin), and
- Clinically significant changes in vital signs.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The statistical analyses were descriptive.

6.2.10 Study Population and Disposition

A total of 42 wounds (38 chronic wounds and 4 induced wounds) in 7 patients were treated with EB-101. Five patients (71.4%) completed the study, and 2 patients (28.6%) discontinued the study during LTFU due to subjects' demise, unrelated to EB-101 treatment. Six chronic control wounds were also analyzed.

6.2.10.1 Populations Enrolled/Analyzed

A total of 7 patients received treatment of the 10 patients who signed consent and entered the Screening period of the study.

6.2.10.1.2 Demographics:

Table 15 outlines the demographics and baseline characteristics for study 31095 participants. The mean age of treated subjects was 28.6 years. Most of the subjects are male (71.4%), and all patients are White (100.0%). Six patients (85.7%) had documented *COL7A1* mutations. One subject's *COL7A1* mutation data was inadvertently not included, but all 7 were *COL7A1* mutation positive due to study enrollment requirements.

Table 15: Demographic and Baseline Characteristics:

Patient Demographic and Baseline Characteristics, Safety Population	Phase 1/2a (N=7)
Age at Parent Study Informed Consent Date (Years)	-
n	7
Mean (SD)	28.6 (9.43)
Median (Min, Max)	31.0 (18, 45)
Gender, n (%)	
Male	5 (71.4)
Female	2 (28.6)
Ethnicity, n (%)	-
Hispanic or Latino	3 (42.9)
Not Hispanic or Latino	4 (57.1)
Not reported	0
Race, n (%)	-
White	7 (100.0)
Black or African American	0
Asian	0
Other	0
Height (cm)	-
n	6
Mean (SD)	172.3 (6.41)
Median (Min, Max)	172.8 (163, 180.34)
Weight (kg)	-
n	6
Mean (SD)	51.3 (6.19)
Median (Min, Max)	52.1 (40.1, 59.2)
BMI (kg/m ²)	-
n	6
Mean (SD)	17.3 (2.11)
Median (Min, Max)	17.3 (14.3, 19.6)
Age of RDEB Diagnosis (months)	-
n	7
Mean (SD)	184.9 (220.64)
Median (Min, Max)	60.0 (0, 523)
Number of wounds treated per patient	-
n	7
Mean (SD)	6.0 (0.00)
Median (Min, Max)	6.0 (6, 6)

Source The reviewer adapted table from Table 7 from 14563/31095 CSR on page 42-43

Abbreviations: BMI, body mass index; COL7A1, collagen type VII alpha 1 chain; Max, maximum; Min, minimum; RDEB, Recessive Dystrophic Epidermolysis Bullosa; SCC, squamous cell carcinoma; SD, standard deviation.

6.2.10.1.3 Subject Disposition

The mean (SD) duration of exposure for all enrolled patients was 6.16 (1.513) years. All subjects received EB-101 treatment and were enrolled into the LTFU study. Two subjects died during the LTFU for reasons unrelated to EB-101 treatment.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s):

The proportion of RDEB wound sites with healing $\geq 50\%$ from Baseline as assessed by IGA were summarized for induced treated, chronic treated, and chronic control wounds. For chronic wounds: 94.7% (36 of 38) of EB-101-treated sites showed $\geq 50\%$ healing from Baseline at both 3-and 6-months post-treatment and 68.4% (26 of 38) at 1 year (Table 16). Similarly, wound healing $\geq 50\%$ from Baseline was seen in 100.0% (4 of 4) of EB-101-treated induced wounds at 3 months post-treatment, 75.0% (3 of 4) at 6 months, and 100.0% (4 of 4) at 1 year. The proportions of treated wounds with healing $\geq 50\%$ from Baseline were higher than those of control wounds at all time points: 33.3% (2 of 6) at 3 months, 0% (0 of 6) at 6 months, 33.3% (2 of 6) at 1 year.

Table 16: Proportion of RDEB Wounds Achieving $\geq 50\%$ Healing From Baseline

Time Point	Chronic (n=38)	Induced (n=4)	Control (n=6)
12 weeks	36/38 (94.7)	4/4 (100.0)	2/6 (33.3)
25 weeks	36/38 (94.7)	3/4 (75.0)	0/6 (0.0)
52 weeks	26/38 (68.4)	4/4 (100.0)	2/6 (33.3)
Year 2	27/38 (71.1)	4/4 (100.0)	1/6 (16.7)
Year 3	18/26 (69.2)	4/4 (100.0)	1/3 (33.3)
Year 4	20/21 (95.2)	3/3 (100.0)	0/2 (0.0)
Year 5	18/27 (66.7)	3/3 (100.0)	1/3 (33.3)

Source: The reviewer adapted from the table 8 of Studies 14563/31095 CSR page 46

Note: The ITT analysis population consists of enrolled patients with any wound sites identified as induced treated, chronic treated (non-induced), or chronic control wounds. All wound sites from the ITT patients are referred to as ITT wounds (Treated Chronic = 38, Treated Induced = 4, and Control = 6).

Abbreviations: ITT, Intention-to-treat.

6.2.11.2 Analyses of Secondary Endpoints

Estimated healed wound size from Baseline for treated RDEB wound sites was summarized categorically at each post-baseline time point for induced treated and chronic treated wounds. The percentage of EB-101-treated chronic wounds with an estimated healed wound size from Baseline of $\geq 30 \text{ cm}^2$ was 81.6% (31 of 38) at 3 months, 65.8% (25 of 38) at 6 months, 39.5% (15 of 38) at 1 year (Table 17). The molecular correction of C7 was assessed by both IF and the presence of AFs. The NC2 domain of C7 or AFs were detected in 6 patients at 3 months post-treatment, 5 patients at 6 months, 3 patients at 1 year, and 2 patients at 2 years.

Table 17: Proportion of RDEB Wounds With Estimated Healing Size of $\geq 30 \text{ cm}^2$ Healing From Baseline

Time Point	Chronic (n=38)	Induced (n=4)
12 weeks	27/38 (71.1)	3/4 (75.0)
25 weeks	22/38 (57.9)	1/4 (25.0)
52 weeks	10/38 (26.3)	2/4 (50.0)
Year 2	20/38 (52.6)	3/4 (75.0)
Year 3	14/26 (53.8)	2/4 (50.0)
Year 4	16/21 (76.2)	2/3 (66.7)
Year 5	10/27 (37.0)	2/3 (66.7)

Source: The reviewer adapted from the table 9 of Studies 14563/31095 CSR page 49

Notes: Estimated healed wound size = (lower limit of wound healing IGA score)/100% × graft size (cm²), where the graft size for this study is 40 cm². For the lower limit of IGA score, complete healing is treated as 100%; <25% healing is treated as 0%. The ITT analysis population consists of enrolled patients with any wound sites identified as induced treated, chronic treated (non-induced), or chronic control wounds. All wound sites from the ITT patients are Chronic = 38, Treated Induced = 4, and Control = 6).

^an1 = Number of wounds in category for healing improvement percentage from Baseline; n2 = Total number of wounds examined in the category.

Abbreviations: ITT, Intention-to-treat.

6.2.11.3 Exploratory Analyses

The percentage of chronic wounds that had ≥75% healing compared with Baseline as assessed by IGA at Months 3, 6, and 12 in the Phase 1/2a study and annually up to the closure of the LTFU study were summarized in Table 18.

Table 18: Proportion of RDEB Wounds Achieving ≥75% Healing From Baseline

Time Point	Chronic (n=38)	Induced (n=4)	Control (n=6)
12 weeks	31/38 (81.6)	4/4 (100.0)	2/6 (33.3)
25 weeks	25/38 (65.8)	3/4 (75.0)	0/6 (0.0)
52 weeks	15/38 (39.5)	4/4 (100.0)	1/6 (16.7)
Year 2	22/38 (57.9)	4/4 (100)	1/6 (16.7)
Year 3	14/26 (53.8)	3/4 (75.0)	0/3 (0.0)
Year 4	18/21 (85.7)	2/3 (66.7)	0/2 (0.0)
Year 5	16/27 (59.3)	3/3 (100.0)	1/3 (33.3)

Source: The reviewer adapted from the table 9 of Studies 14563/31095 CSR page 47

Abbreviations: ITT = Intention-to-treat.

Note: The ITT analysis population consists of enrolled patients with any wound sites identified as induced treated, chronic treated (non-induced), or chronic control wounds. All wound sites from the ITT patients are referred to as ITT wounds (Treated Chronic = 38, Treated Induced = 4, and Control = 6).

^a n1 = Number of wounds in category for healing improvement percentage from Baseline; n2 = Total number of wounds examined in the category.

Other exploratory efficacy endpoints assessed at Baseline and Months 3, 6, and 12 in the Phase 1/2a study and annually up to the closure of the LTFU were the proportion of wound sites which subjects reported improvement of pain, itching, durability of treated wounds, and ease of blistering. Reporting pain and itching was based on binary outcome measure of yes versus no. Additionally, for durability and ease of blistering, subjects were to indicate more, less or no change.

Reviewer Comment:

This study was designed as an initial, exploratory study to provide safety and preliminary efficacy data. Given its exploratory design, the study has several limitations to data interpretation including its non-randomized design, the potential for bias in the investigator's assessment of wound healing, and the high risk of bias inherent to patient-reported outcomes in a design that is not concurrently controlled and randomized.

Despite these limitations which are inherent to early phase, exploratory studies, the results demonstrate that EB-101 treatment had a favorable effect on wound healing in most treated wounds to a point exceeding the healing rates observed in the control wounds used for comparison. Even though these comparisons are descriptive and without a prespecified analysis plan or study powering for efficacy, the favorable

results align with the phase 3 trial results and are supportive of the favorable treatment effect of EB-101 on wound healing in RDEB.

6.2.12 Safety Analyses

6.2.12.1 Overview of Adverse Events

There were 121 total TEAEs that were reported in 7 (100%) patients (Table 19):

- 14 TEAEs in 4 (57.1%) patients were serious (4 SAEs of SCC in 2 patients; 3 SAEs of anemia in 2 patients; 2 SAEs of failure to thrive in 2 patients; and 1 SAE each of metastatic SCC, cellulitis, enterocolitis infectious, sepsis, and menorrhagia in 1 patient. Four (4) TEAEs in 2 (28.6%) patients led to hospitalization or prolonged hospitalization, 1 event each of anemia, cellulitis, failure to thrive, and menorrhagia in 1 patient.
- 12 TEAEs in 5 (71.4%) patients were related to EB-101: 4 TEAEs of procedural pain in 4 patients; 3 TEAEs of local reaction in 1 patient; 2 TEAEs of wound infection in 2 patients; and 1 TEAE each of blood immunoglobulin G increased, blood immunoglobulin A increased, and pruritis in 1 patient and 31 TEAEs in 7 (100.0%) patients were infections.

All 7 subjects experienced a total of 121 Treatment Emergent Adverse Events. Based on organ class, subjects experienced the following: 100% (7) of subjects had 31 events of wound infections/infestations, 28.6% (2) of subjects had 18 events of neoplasms benign, malignant and unspecified (including cysts and polyps), 100% (7) of subjects had 15 events of gastrointestinal disorders, 71.4% (5) of subjects had 11 events of blood and lymphatic system disorders, 57.1% (4) of subjects had 8 events of injury, poisoning and procedural complications, 42.9% (3) of subjects had 7 events of general disorders and administration site conditions, 71.4% (5) of subjects had 7 events of psychiatric disorders, 42.9% (3) of subjects had 6 events of metabolism and nutrition disorders, 28.6% (2) of subjects had 5 events of respiratory, thoracic and mediastinal disorders, 42.9% (3) subjects had 3 events of pruritis, 9.1% (1) subject each experienced elevated immunoglobulin G, elevated immunoglobulin A, paresthesia, presyncope, tinnitus, hypothyroidism, vision blurred, extremity pain, hematuria and menorrhagia.

Table 19: Overall summary of TEAEs

Category	Overall (N=7)
All TEAEs	-
Number of Patients, n (%)	7 (100.0)
Number of Events	121
Serious TEAEs	-
Number of Patients, n (%)	4 (57.1)
Number of Events	14
TEAEs Leading to New or Prolonged Hospitalization	-
Number of Patients, n (%)	2 (28.6)
Number of Events	4
TEAEs Related to EB-101 ^a	-
Number of Patients, n (%)	5 (71.4)
Number of Events	12
TEAEs Leading to Death	-
Number of Patients, n (%)	2 (28.6)
Number of Events	2
TEAEs of Infection	-
Number of Patients, n (%)	7 (100.0)
Number of Events	31

Source: Adapted from Study 14563/31095 CSR Table 12, page 58

Notes: TEAEs are defined as any adverse event with an onset on or after the date of EB-101 application.

^a Possible, Probable, and Definitely Related are considered Related to EB-101; a missing relationship will conservatively be considered Related to EB-101 as well.

Abbreviations: SAE, serious adverse event; TEAEs, treatment-emergent adverse events

Treatment-Emergent Wound Adverse Events :

There was a of 12 total TEWAEs reported in 11 (26.2%) treated wounds. Of these, 9 TEWAEs were related to treatment (5 events of local reaction in 2 patients, 2 events of wound infection in 1 patient, and 2 events of pruritis in 1 patient). There were 5 TEWAEs of infections. No TEWAEs were reported in control wounds (n=6) and there were no serious TEWAEs.

The most frequently reported TEWAEs were as follows: among treated chronic wounds were 4 TEAEs of local reaction reported in 4 (10.5%) wounds, 4 TEAEs of wound infection reported in 4 (10.5%) wounds, and 1 TEAE of pruritus was reported in 1 (2.6%) wound. Among treated induced wounds, local reaction was reported in 1 (25.0%) wound, localized infection was reported in 1 (25.0%) wound, and pruritus was reported in 1 (25.0%) wound.

6.2.12.2 Deaths

There were 2 TEAEs that resulted in death.

Patient: (b) (6) 18-year-old male who was diagnosed with RDEB at birth. He had a complex medical history including esophageal stricture, corneal abrasion, pruritis, failure to thrive with gastric tube dependence, pseudosyndactyly, chronic pain and leg contractures. His baseline laboratory data was significant for leukocytosis with neutrophilia, anemia, and thrombocytosis. He received EB-101 to 6 wounds (5 chronic and 1 induced wound) on (b) (6). His baseline wound assessment revealed multi-microbial infection of an upper extremity wound. On post treatment Study Day 2497, he

was admitted to intensive care unit due *Klebsiella* septic shock and treated with intravenous antibiotics. He was converted to comfort care. He died on Study Day 2503. The event was assessed as unrelated to EB-101 treatment, likely due to disease progression.

Reviewer's Comment:

- *The reviewer agrees with the investigator's assessment. The subject died due to complications from septic shock.*

Patient (b) (6) 32-year-old female who was diagnosed with RDEB at 27 years of age. Her medical history is significant for chronic pain, esophageal strictures, failure to thrive, SCC of right forearm and knee, melanoma of left lateral thigh. She received EB-101 to 6 wounds (5 chronic and 1 induced wound). Her baseline laboratory data was significant for anemia and thrombocytosis. Throughout the study period she experienced multiple SCC events (right forearm, left dorsal wrist, right thigh, left radial hand, left forearm and right knee) which were assessed as Grade 2 SCC with successful resections. On Study Day 1323 she was diagnosed with Grade 3 SCC to the right ulnar wrist and left forearm. A chest computed tomography revealed metastatic SCC. Due to positive margins following excision of right ulnar lesion she declined chemotherapy. On Study Day 1396 she developed failure to thrive and placed on hospice care. She died due to failure to thrive on Study Day 1406.

All development of SCC were noted on non-EB-101 treated wounds, therefore all events of SCC were assessed unrelated to EB-101 treatment and likely due to the underlying disease.

Reviewer's Comment:

- *The review agrees with the investigator's assessment. The subject died due to FTT following development of SCC that was untreated with evidence of metastasis. It is important to note, the metastatic SCCs were not investigated for presence of proviral DNA.*

6.2.12.3 Nonfatal Serious Adverse Events

There were 14 non-fatal SAEs occurring in 4 subjects. See Table 20. None of these SAEs were assessed as related to EB-101. There were no serious TEWAEs.

Table 20: Treatment-Emergent Serious Adverse Events

System Organ Class Preferred Term	Overall (n=7) Subjects n (%)	Overall (n=7) Events
All Serious TEAEs	4 (57.1)	14
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 (28.6)	5
Metastatic SCC	1 (14.3)	1
SCC	2 (28.6)	4
Blood and Lymphatic System Disorder	2 (28.6)	3
Anemia	2 (28.6)	3
Infection and Infestations	3 (42.9)	3
Cellulitis	1 (14.3)	1
Enterocolitis	1 (14.3)	1
Sepsis	1 (14.3)	1
Metabolism and Nutrition Disorders	2 (28.6)	2
Failure to thrive	2 (28.6)	2
Reproductive System and Breast Disorders	1 (14.3)	1
Menorrhagia	1 (14.3)	1

Source Reviewer adapted from Tables and Figures of EB-101-Phase 1/2a (14563 and 31095), Table 14.3.1.1.5.

Adverse events were coded using MedDRA version 23.0. TEAE = Treatment-Emergent Adverse Event.

Treatment-emergent adverse events (TEAEs) are defined as any adverse event with an onset on or after the date of EB-101 application.

Subject (b) (6) 32-year-old female who was diagnosed with RDEB at 27 years of age. Her medical history is significant for chronic pain, esophageal strictures, failure to thrive, SCC of right forearm and knee, melanoma of left lateral thigh. She received EB-101 to 6 wounds (5 chronic and 1 induced wound). She experienced multiple serious TEAEs

- Menorrhagia: On Study Day 975, the subject was diagnosed with Grade 3 menorrhagia secondary to a non-serious Grade 2 uterine fibroid. The subject was hospitalized where she underwent an embolization of the uterine fibroid. She was also treated with estrogen, norethindrone and transfusion with packed red blood cells. The anemia resolved and subject was discharged.
- Cellulitis of the right arm: On Study Day 1200 subject developed Grade 3 cellulitis of right arm at the site of an SCC excision. The subject was treated with antibiotic. With negative blood cultures she was discharged with a course of oral antibiotic therapy.
- SCC: On Study Day 1323 subject was diagnosed with Grade 3 SCC to the right ulnar wrist and left forearm. The left arm was resected but discovered to have positive margins. In addition, a chest computed tomography showed metastatic SCC. Subject declined chemotherapy, so the events were not resolved at the time of subject's death.
- Failure to thrive: On Study Day 1396 subject was diagnosed with failure to thrive. She was admitted to hospice care. With a 40-lb weight loss from diarrhea.

Reviewer's Comment:

- *The subject's clinical course was complicated by multiple SAEs. The etiology of menorrhagia was a Grade 2 uterine fibroid. The subject has a history of anemia like due to menorrhagia from the uterine fibroids. The subject develops cellulitis at a wound site created because of an SCC excision. SCC is a known complication of RDEB. The subject's medical history is significant for the development of SCC. Of note, the SCC sites were areas not treated with EB-101. The subject also experienced failure to thrive, which she has a history of prior to exposure to EB-101. The recurrent failure to thrive episode occurred in the setting of metastatic SCC for which she declined chemotherapy.*
- *The reviewer agrees with the investigator that the events of menorrhagia, cellulitis, SCC, and failure to thrive are all unrelated to EB-101 treatment.*

Subject (b) (6) 32-year-old white male diagnosed with RDEB at 32 years of age. He received EB-101 to 6 wounds (5 chronic and 1 induced wound). On Study Day 859 he was diagnosed with Grade 3 metastatic SCC to the right forearm and in aright axillary lymph node. He received cemiplimab and radiation therapy, with resolution evidenced by a clear positron emission tomography (PET) scan. On Study Day 1242, the patient was diagnosed with Grade 3 SCC on the right back. The lesion was excised, and subject was treated with chemotherapy. On Study Day 1789 he was diagnosed with Grade 3 SCC on the right flank which was also treated with cemiplimab. Neither the right back nor right flank SCC were resolved.

Reviewer's Comment:

- *None of these lesions were associated with a wound site treated with EB-101. Therefore, reviewer agrees with investigator's assessment that these lesions are not related to EB-101.*

Subject (b) (6) 31-year-old male diagnosed with RDEB at 5 years of age. He received EB-101 treatment to 6 wounds (5 chronic and 1 induced wounds). His medical history is significant for anemia, esophageal stenosis, thrombocytosis, and constipation. On Study Day 1094 and 1446 he was diagnosed with episodes of life-threatening anemia which resolved with transfusion of packed red blood cells. On Study Day 2099 while hospitalized for SCC excision, he was diagnosed with Grade IV *Clostridium difficile* (*C.Diff*) infection. A CT scan confirmed *C.Diff* infection. He was treated with antibiotics with resolution.

Reviewer's Comment:

- *C.Diff infections are common in subjects with prolonged hospitalization or antibiotic use. Subjects with RDEB are commonly exposed to antibiotics. The reviewer agrees with investigator's assessment of that the event of enterocolitis from C.Diff is unrelated to EB-101 treatment.*

Subject (b) (6) See [section 6.2.12.3](#) for SAE on severe sepsis and failure to thrive.

6.2.12.4 Adverse Events of Special Interest (AESI)

Not applicable

6.2.12.5 Clinical Test Results

There were 8 clinically significant laboratory values, 6 were severe and 2 were life-threatening or debilitating. The most frequently occurring clinically significant laboratory abnormality was anemia. All subjects had baseline anemia and majority had evidence of thrombocytosis on laboratory evaluation prior to exposure to EB-101.

There were no clinically meaningful changes associated with treatment were observed in vital signs, or physical examination findings.

6.2.12.6 Dropouts and/or Discontinuations

None

6.2.13 Study Summary and Conclusions

Study 14563 was a first-in-human, Phase 1/2a, single center, open-label, proof-of concept study that evaluated the long-term efficacy and safety of EB-101 in ≥ 13 -year-old RDEB subjects. Study 31095 was the LTFU to this Phase 1/2a study. Ten subjects were enrolled, and 7 subjects were treated. Five subjects completed the study, 2 subjects died during the LTFU (Study 31095) period. Forty-two wounds (38 chronic and 4 induced) and 6 control chronic wounds were treated and analyzed.

The proportion of wounds achieving $\geq 50\%$ healing from Baseline was higher than in the control group throughout the study up until Year 5. Furthermore, a majority of EB-101 treated wounds had an estimated healed wound from Baseline of size $\geq 30\text{cm}^2$ and the NC2 domain of C7 and/or AF were detected in 2 subjects at Year 2 post treatment.

There was a total of 121 TEAEs in these studies. There were 14 SAEs, but no SAEs were assessed as related to EB-101. The SAEs ranged from moderate to life-threatening or debilitating. Twelve TEWAEs were reported in 11 wounds in 5 subjects which ranged from mild to moderate. 9 TEWAEs were due to local reaction, wound infection and pruritis which were all attributed to EB-101. There were no serious TEWAEs. Wound infections and pruritis are common in RDEB wounds. Circulating antibody to C7/C7 immune complexes were conducted in 5/7 subjects which were negative after EB-101 treatment. All subjects were tested for cytotoxic T cell activity after EB-101 treatment which were negative. The overall safety assessments from the Phase 1/2a study were reassuring.

The preliminary clinical efficacy in the Phase 1/2a study suggests clinical benefit of EB-101 in RDEB wounds that persisted after the 1-year endpoint assessment period in several suggesting durability of effect. Some however, due to the limitations of study including open-label, lack of randomization, small size, and reliance of investigator's assessment of efficacy, the Phase 1/2a study was considered exploratory.

6.3 Trial #3

EB-101-LT-001: This is a LTFU study in RDEB subjects previously treated with EB-101 in interventional studies (14563/31095 and EB-101-CL-301).

6.3.1 Objectives:

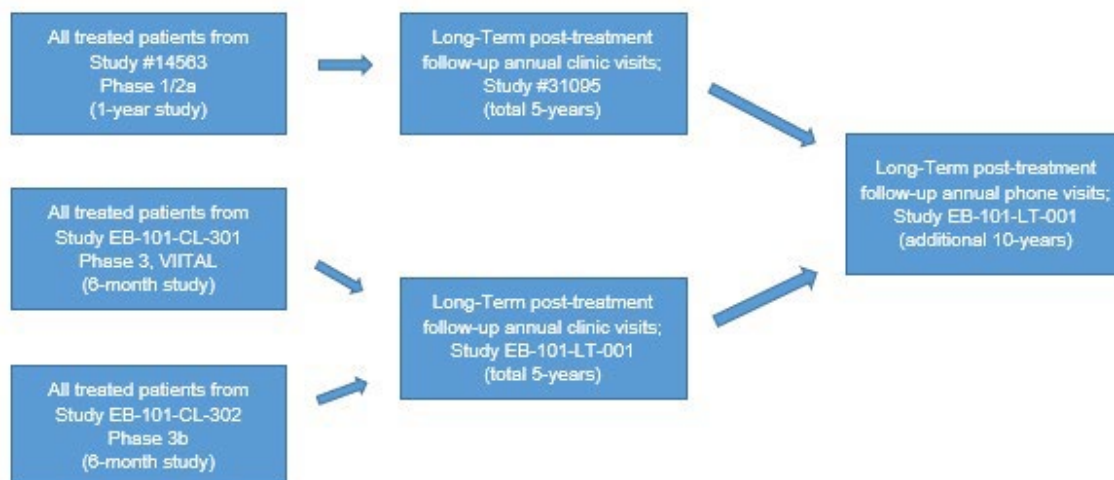
The objective of this study is to evaluate the long-term efficacy and safety of EB-101 in subjects who received EB-101 treatment for RDEB.

6.3.2 Design Overview

Subjects previously treated in the Phase 3 study (EB-101-CL-301; VIITAL; a 6-month study) are seen in the clinic at Months 6, 18, 30, 42, and 54 which corresponds to Years 1, 2, 3, 4, and 5 after initial surgical application of EB-101. Upon completion of the clinic visits for 5 years, patients will have an annual telephone interview for an additional 10 years, up to 174 months (i.e., 15 years post-treatment).

Similarly subjects previously treated with EB-101 in the Phase 1/2a study (14563/31095 EB-101) and already followed for a minimum of 5 years in the LTFU study (31095 LTFU EB-101) had annual telephone interviews beginning approximately 12 months after their last annual visit in Study LTFU EB-101, for a total duration of approximately 15 years. There will be no efficacy assessments performed during the current study (EB-101-LT-001) since they already completed efficacy assessments in the prior study. See schematic Figure 1.

Figure 1 Study Schema



6.3.3 Population

Inclusion Criteria:

1. Willing and able to give consent/assent
2. If under the age of 18, guardian(s) is/are willing and able to give consent
3. Prior study treatment with EB-101.

Exclusion Criteria:

1. Inability to properly follow protocol assessments as determined by the Principal Investigator.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Additional EB-101 treatment is not administered in this study. Table 21 lists assessments conducted throughout the study.

6.3.5 Surveillance/Monitoring

Table 21: Schedule of Assessment:

Procedure	Clinic Visit A *	Clinic Visit B	Clinic Visit C	Phone Call D
Informed consent	X	-	-	-
Inclusion/exclusion criteria	X	-	-	-
Medical history	X	-	-	-
Concomitant medications	X	X	X	X
Concomitant procedures	X	X	X	X
Adverse events	X	X	X	X
Wong-Baker FACES	X	X	X	-
QOLEB	-	X	-	-
CrGI (pain)	X	X	-	-
ZBI-12	-	X	-	-
Physical examination	X	X	-	-
Wound-dressing change	X	X	X	-
Vitals including height and weight	X	X	-	-
Direct investigator assessment of wound healing	X	X	X	-
Canfield imaging of wounds	X	X	-	-
Laboratory tests ^a	X	X	-	-
RCR assay	X	X	-	-

Source: Reviewer adapted from EB-101-LT-001 CSR page: 11

Clinic Visit A = Visit 1 which corresponds to Day 1 (±2 months)

Clinic Visit B = Visits 2,4,6,7,8 which corresponds to Months 6, 18, 30, 42, 54 (±14 days)

Clinic Visit C = Visits 3, 5 which corresponds to Months 12, 24 (±14 days)

Phone call D = Phone Visits 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 which corresponds = Months 66, 78, 90, 102, 114, 126, 138, 150, 162, 174 (±14 days)

Phase 1/2a study start from Visit 9 up to Visit 18; informed consent was collected before conducting any procedures in the current study.

* Subjects enrolled <2 months after completing Week 24 in the Phase 3 study may be Visit 1/Day 1 and did not need to be repeated.

^a Laboratory test included CBC, CMP, total and direct bilirubin, pre-albumin, and CRP.

Abbreviations: CBC, complete blood count; CrGI, Caregiver's Global Impression; CMP, complete metabolic panel; CRP, C-reactive protein; EB, epidermolysis bullosa; PI, Principal Investigator; PRN, as needed; PRO, Patient-reported outcomes; QOLEB, Quality of Life in Epidermolysis Bullosa; RCR, replication-competent retrovirus; ZBI-12, Zarit Burden Interview 12-item version.

6.3.6 Endpoints and Criteria for Study Success

Efficacy:

- Primary investigator's wound healing assessment
- Wong-Baker FACES scale pain reduction assessment
- Itch severity scores

- Zarit Burden Interview Short Form (ZBI-12) – Caregiver wound care
- Quality of Life in Epidermolysis Bullosa (QOLEB) questionnaire
- Caregiver Global Impression of Pain (CrGI-Pain)

Safety:

- Treatment-emergent adverse events (TEAEs)
- Wounds that result in hospitalization
- Wounds that have an infection or any related AE
- Squamous cell carcinoma
- Replication-competent retrovirus (RCR) status

6.3.7 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were used.

6.3.8 Study Population and Disposition

15 patients were enrolled, 10 from the Phase 3 study and 5 from the Phase 1/2a study. Only 5 of the 7 patients in the Phase 1/2a study were enrolled in the LTFU study because 2 subjects died in the Phase 1/2a study. Table 22 outlines the demographic and baseline characteristics of all subjects across the 3 studies.

6.3.8.1 Populations Enrolled/Analyzed

The study planned to enroll 22 subjects; 15 subjects were analyzed.

6.3.8.1.2 Demographics

Table 22: Demographic and Baseline Characteristics

Characteristic ^a	Overall (N=15)
Age (years)	-
n	15
Mean (SD)	28.9 (9.65)
SE	2.49
Median	27.0
Min, Max	17, 50
Sex, n (%)	-
Male	8 (53.3)
Female	7 (46.7)
Ethnicity, n (%)	-
Hispanic or Latino	4 (26.7)
Not Hispanic or Latino	10 (66.7)
Not Reported	1 (6.7)
Race, n (%)	-
White	15 (100.0)
Height (cm)	-
n	15
Mean (SD)	167.15 (10.236)
SE	2.643
Median	168.20
Min, Max	147.0, 182.7
Weight (kg)	-
n	15
Mean (SD)	51.16 (12.178)
SE	3.144
Median	51.80
Min, Max	30.0, 75.6
BMI (kg/m ²)	-
n	15
Mean (SD)	18.50 (5.284)
SE	1.364
Median	16.88
Min, Max	10.4, 33.4
Number of Wounds Treated Per Patient in Parent Studies ^b	-
n	15
Mean (SD)	5.4 (0.99)
SE	0.25
Median	6.0
Min, Max	3, 6

Source: Reviewer adapted table from EB-101-LT-001 CSR, page 17-18

^a Age is upon informed consent date of EB-101-LT-001, Height/Weight/BMI are last non-missing measurement before EB-101 application.

^b Number of wounds treated in parent studies includes induced wounds, chronic wounds treated in the Phase 1/2a study and randomized and non-randomized treated wounds in the Phase 3 study

Abbreviations: BMI, body mass index, SD, standard deviation, SE, standard error

6.3.8.1.3 Medical/Behavioral Characterization of the Enrolled Population

All subjects were diagnosed with RDEB and previously treated with EB-101. The most frequently reported medical history in more than 50% of the subjects were: esophageal perforation, anemia, pruritus, constipation, gastroesophageal reflux disease, wound infection, and corneal abrasion.

6.3.8.1.4 Subject Disposition

See [section 6.3.10](#)

6.3.9 Efficacy Analyses

6.3.9.1 Analyses of Primary Endpoint(s)

EB-101-CL-301:

The proportion of randomized wounds achieving $\geq 50\%$ and $\geq 75\%$ healing was greater in the randomized treated wounds compared with the randomized control wounds in the ITT population as follows (Table 23):

- Month 6 (Month 12 post-treatment) $\geq 50\%$ wound healing in 78.9% versus 10.5% of wounds and $\geq 75\%$ wound healing in 52.6% versus 10.5%; and was statistically significant with $p=0.0001$ and $p=0.0163$, respectively
- Month 12 (Month 18 post-treatment) $\geq 50\%$ in 60.0% versus 13.3% of wounds and $\geq 75\%$ wound healing in 53.3% versus 6.7%; and was statistically significant with $p=0.0154$ and $p=0.0155$, respectively
- Month 18 (Month 24 post-treatment) $\geq 50\%$ wound healing in 75.0% versus 12.5% of wounds and $\geq 75\%$ wound healing in 75.0% versus 12.5%; $p=0.0615$ for each wound healing category.

Table 23: Proportion of RDEB Wounds by Healing Category and Clinic Visit

Visit	^a Randomized Treated (N=41)	^a Randomized Control (N=41)	Randomized Wound Pairs (N=41)
Month 6 (12 months post treatment (n1/n2) ^c	-	-	-
≥50% - <75% of Baseline 2-sided P-wave	5/19 (26.3)	0/19 (0.0)	0.0001
≥75% - <100% of Baseline 2-sided P-wave	10/19 (52.6)	2/19 (10.5)	0.0163
Month 12 (18 months post treatment (n1/n2) ^c	-	-	-
≥50% - <75% of Baseline 2-sided P-wave	1/15 (6.7)	1/15 (6.7)	0.0154
≥75% - <100% of Baseline 2-sided P-wave	8/15 (53.3)	1/15 (6.7)	0.0155
Month 18 (24 months post treatment (n1/n2) ^c	-	-	-
≥50% - <75% of Baseline 2-sided P-wave	0/8 (0.0)	0/8 (0.0)	0.0615
≥75% - <100% of Baseline 2-sided P-wave	6/8 (75.0)	1/8 (12.5)	0.0615

Source: Reviewer adapted from EB-101-LT-001 CSR page 22-23

^a All randomized wound pairs were in 10 patients that were treated on Day 0 within the Phase 3 study (EB-101-CL- 301)

^b Baseline is defined as the most recent, non-missing, pre-treatment assessment, where pre-treatment may include visits from a previous parent study. Months refer to the time in EB-101-LT-001 study.

^c n¹ = number of wounds in category for healing improvement percentage from Baseline; n² = total number of wounds with non-missing healing improvement category.

Abbreviations: ITT, intention-to-treat; RDEB, recessive dystrophic epidermolysis bullosa.

The mean (±SD) pain reduction by the Wong-Baker FACES scale was greater for the randomized treated wounds compared with the randomized control wounds as follows:

- Month 6 (Month 12 post-treatment): 2.11 ± 3.680 versus 1.16 ± 1.922
- Month 12 (Month 18 post-treatment): 2.27 ± 4.590 versus 2.00 ± 3.762
- Month 18 (Month 24 post-treatment): 2.67 ± 4.697 versus 0.83 ± 2.329.

The mean pairwise difference across patients in pain reduction was 0.95 at Month 6 (Month 12 post-treatment), 0.57 at Month 12 (Month 18 post-treatment), and 1.83 at Month 18 (Month 24 post-treatment); the differences were not statistically significant between the randomized treated and control wounds at Months 6, 12, and 18.

At Month 6 (Month 12 post treatment), the mean (±SD) longitudinal change in Zarit Burden Interview 12-item version (ZBI-12) scores related to wound care was -2.50 ± 2.646. At Month 6 (Month 12 post treatment), caregivers assessed randomized treated wounds in 3 of 5 subjects as much improved” (CrGI-Pain scores) compared with a “very much improved” assessment of randomized control wounds in 1 of 5 patients.

Reviewer Comment:

- Although the long-term results of EB-101-CL-301 indicates a positive trend, the statistical analysis for the efficacy results were descriptive. Therefore, the sponsor's calculation on p-values is misleading due to the lack of hypothesis testing. Furthermore, the open-label design of this study and subjectivity of the questionnaires (ZBI and CrGI) makes interpretation of the efficacy data difficult.

6.3.9.2 Dropouts and/or Discontinuations

None

6.3.10 Safety Analyses

6.3.10.1 Overview of Adverse Events

Fifteen subjects were enrolled into the LTFU study. Table 24 lists the 47 TEAEs observed overall. A total of 6 subjects (40.0%) had 10 serious TEAEs with 3 patients (20.0%) who had 6 TEAEs that led to new or prolonged hospitalization. A total of 6 patients (40.0%) had 14 TEAEs of infection overall. No TEAEs were considered related to EB-101 and none were fatal. No TEAEs led to treatment discontinuation. There were no TEAEs in the randomized treated wounds.

Table 24: Overall Summary of TEAEs ^a

Category, n (%)	Overall (N=15)
All TEAEs	-
Number of Subjects, n (%)	10 (66.7)
Number of Events	47
Serious TEAE	-
Number of Subjects, n (%)	6 (40.0)
Number of Events	10
TEAEs leading to Prolonged Hospitalization	-
Number of Subjects, n (%)	3 (20.0)
Number of Events	6
TEAEs of Infection	-
Number of Wounds, n (%)	6 (40.0)
Number of Events	14

Source: Reviewer adapted from EB-101-LT-001 CSR page 30

Study wound AEs are not included in this table and are summarized separately.

^a TEAEs of infection includes all preferred terms under SOC of Infections and Infestations.

Abbreviations: TEAE, treatment-emergent adverse event; SOC, system organ class.

The most common TEAEs (occurring in ≥ 2 patients) which were wound infection (26.7%), procedural pain (13.3%), squamous cell carcinoma (20.0%; includes was squamous cell carcinoma of skin in 1 patient), insomnia (13.3%), and anemia (13.3%).

6.3.10.2 Deaths

None

6.3.10.3 Nonfatal Serious Adverse Events

Six subjects experienced 14 serious TEAEs.

Table 25: Serious TEAEs: Safety Population

Patient ID	Preferred Term	Led to New or Prolonged Hospitalization (Y/N)	Severity	Relationship to EB-101	Outcome
(b) (6)	2 events of Ascites	Yes	Severe	Unlikely related	Recovered/Resolved
(b) (6)	Vena cava thrombosis	Yes	Severe	Unrelated	Recovered/Resolved
(b) (6)	SCC	No	Severe	Unrelated	Recovered/Resolved
(b) (6)	2 events of wound infection	Yes	Severe	Unrelated	Recovered/Resolved
(b) (6)	Staphylococcal wound infection	Yes	Severe	Unrelated	Recovered/Resolved
(b) (6)	SCC	No	Severe	Unrelated	Recovered/Resolved
(b) (6)	2 events of SCC	No	Severe	Unrelated	Ongoing

Source: Reviewer adapted from EB-101-LT-001 CSR, Table 12, Page 34

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAEs = treatment-emergent adverse events. Notes: AEs were coded using MedDRA version 23.0

Reviewer's Comment:

- The events of SCC and wound infection are commonly associated with RDEB disease course. The SCCs were not seen in any EB-101 treated wounds. The wound infections occurred at least 6 months after the application of EB-101, entry period into the LTFU study. Therefore, it is unlikely to be related to EB-101 due to lack of temporal relationship with the treatment and development of infection. Furthermore, subject (b) (6) experienced vena cava thrombosis and 2 events of ascites more than 2 years post treatment. This subject has a significant and complex ongoing medical history with multiple comorbidities. Given the timing of the AEs in the setting of the subject's medical history these events are unlikely related to EB-101. Reviewer agrees with investigator's assessment that these events are unrelated to EB-101 treatment.*

6.3.10.4 Clinical Test Results

Every subject had abnormal laboratory data such as anemia and elevated c-reactive protein (CRP) at baseline. Many subjects demonstrated persistent laboratory data abnormalities without significant clinical manifestations. One subject (b) (6) had clinically significant low hemoglobin. No notable changes in vital signs or physical examination abnormalities were observed during the study.

6.3.10.5 Dropouts and/or Discontinuations

There were no AEs that led to discontinuation and/or dropouts.

6.3.11 Study Summary and Conclusions

EB-101-LT-01 is an ongoing LTFU study for previously treated RDEB subjects from Studies 14563/31095 EB-101 and EB-101-CL-301. Overall, the efficacy data, which was based on descriptive statistics, demonstrated durability of effect post treatment, with higher proportion of randomized treated wounds achieved $\geq 50\%$ and $\geq 75\%$ wound healing, pain reduction and improved care giver assessment of wound than randomized control wounds.

The safety profile was reassuring. EB-101 was well tolerated. Although incidence of serious TEAS was 40% serious, with the majority being SCCs, none of these SCC were at the EB-101 treated wound sites. There were no TEAEs or TEWAEs that were assessed as related to EB-101 treatment. The studies have demonstrated EB-101 has a favorable long-term risk/benefit profile.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1.1 Methods of Integration

There was no integrated overview of efficacy as data were not pooled from the Phase 1/2a (14563/31095) and Phase 3 (EB-101-CL-301) studies due to the differences in major design elements including the design (randomized vs not), nature of wounds (induced treated, chronic treated and control wounds), and methods of ascertainment of treatment response.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

A pooled analyses of safety data from subjects treated with EB-101 in both the Phase 1/2a (14563/31095), Phase 3 (EB-101-CL-301), and the LTFU Study (EB-101-LT-001) was conducted. TEAEs were defined similarly for all 3 studies: in Study 14563/31095 EB-101, TEAEs were defined as AEs that occurred or worsened after the date of EB-101 application. In Study EB-101-LT-001, TEAEs were defined as any AE with an onset date on or after the date of the treatment of randomized wound pairs in Study EB-101-CL-301. TEAEs were considered related to EB-101, by the investigator, if there is a reasonable possibility and recorded on the CRF as 'Possible', 'Probable', and 'Definitely'.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 26: Studies/Clinical Trials Used to Evaluate Safety

Phase	Study Number	Study Design
1/2a	Protocol 14563/LTFU Protocol 31095	Open-label, single-center long-term safety, and efficacy study 7 (5 males and 2 females subjects): 18-45 years old 42 grafted wounds: -38 chronic treated -4 induced treated -6 control wounds
3	EB-101-CL-301	Phase 3, multicenter, open-label study, randomized and intra-patient-controlled study on efficacy and safety of EB-101 compared to SOC in 1:1 fashion. 11 (4 males and 7 female subjects) ≥6 years old -43 randomized treated wounds, -43 randomized control wounds, -14 non-randomized treated wounds
LTFU	EB-101-LT-001	LTFU safety and efficacy study of subjects who participated in a previous clinical trial EB-101 treatment for RDEB ≥6 years old 16 subjects from previous EB-101 studies (8 females and 8 males)

Source: Reviewer adapted from summary of clinical safety 120 safety update report, Table 1: Pages: 6-8

Abbreviations: LTFU, long-term follow-up; NC1+, non-collagenous region 1 of the type VII collagen molecule; RDEB, recessive dystrophic epidermolysis bullosa.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 27: Patient Demographic and Baseline Characteristics

Phase	Phase 1/2a (N=7)	Phase 3 (N=11)	Total (N=18)
Age at Parent Study Informed Consent Date (Years)	-	-	-
n	7	11	18
Mean (SD)	28.6 (9.43)	22.5 (9.10)	24.8 (9.46)
Median (Min, Max)	31.0 (18, 45)	21.0 (6, 40)	23.0 (6, 45)
Gender, n (%)			
Male	5 (71.4)	4 (36.4)	9 (50.0)
Female	2 (28.6)	7 (63.6)	9 (50.0)
Ethnicity, n (%)			
Hispanic or Latino	3 (42.9)	2 (18.2)	5 (27.8)
Not Hispanic or Latino	4 (57.1)	8 (72.7)	12 (66.7)
Not Reported	0	1 (9.1)	1 (5.6)
Race, n (%)			
White	7 (100.0)	10 (90.9)	17 (94.4)
Black or African American	0	0	0
Asian	0	0	0
Other	0	1 (9.1)	1 (5.6)
Height (cm)	-	-	-
n	6	11	17
Mean (SD)	172.3 (6.41)	159.0 (21.72)	163.7 (18.72)
Median (Min, Max)	172.8 (163, 180.34)	164.0 (101.6, 182.7)	168.2 (101.6, 182.7)
Weight (kg)	-	-	-
Pruritis	6	11	17
Mean (SD)	51.3 (6.19)	48.3 (18.39)	49.3 (15.02)
Median (Min, Max)	52.1 (40.1, 59.2)	48.2 (12.1, 75.6)	51.8 (12.1, 75.6)
BMI (kg/m ²)	-	-	-
n	6	11	17
Mean (SD)	17.3 (2.11)	18.6 (6.39)	18.2 (5.23)
Median (Min, Max)	17.3 (14.3, 19.6)	16.9 (10.4, 33.4)	16.9 (10.4, 33.4)
Age at Parent Study RDEB Diagnosis Date	-	-	-
n	7	11	18
Mean (SD)	184.9 (220.64)	63.9 (123.14)	110.9 (172.57)
Median (Min, Max)	60.0 (0, 523)	0.0 (0, 372)	0.0 (0, 523)
Number of Wounds Treated	-	-	-
n	7	11	8
Mean (SD)	6.0 (0.00)	5.2 (1.08)	5.5 (0.92)
Median (Min, Max)	6.0 (6, 6)	6.0 (3, 6)	6.0 (3, 6)

Source: Reviewer adapted from 120-Day safety update report, page: 12-13

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; RDEB, recessive dystrophic epidermolysis bullosa; SCS, Summary of Clinical Safety; SD, standard deviation; SE, standard error.

Table 28: Summary of Exposure to EB-101, Safety Analysis Set

Total Exposure Time (months)	Phase 1/2a	Phase 3	Total
N	7	11	18
Mean (SD)	86.14 (23.37)	25.62 (10.34)	49.16 (34.31)
Median	83.70	23.60	38.20
Min, Max	46.20, 119.70	12.1, 43.10	12.10, 119.70

Source: Reviewer adapted from 120-Day Safety Update Report. Page 9-10.

For Phase 1/2a (i.e., Study 14563 EB-101/31095 LTFU EB-101), Phase 3 (i.e., Study EB-101-CL-301), and the overall (total) columns, the total exposure time (months) is calculated using (last follow-up visit date – parent study EB-101 application date + 1) divided by (365/12)

8.2.3 Categorization of Adverse Events

All reported terms (investigator descriptions) for AEs from all 3 studies were coded using the same version of the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0).

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

None

8.4 Safety Results

8.4.1 Deaths

There were 2 TEAEs with fatal outcomes, both of which occurred in Study 14563/31095. See [section 6.2.12.3](#) for full description.

8.4.2 Nonfatal Serious Adverse Events

There were new serious adverse events (SAE) reported in Study EB-101-LT-001. Table 29 lists study-specific summary of SAEs from Study EB-101-LT-001 as of the 120-Day update.

Table 29: Serious Adverse Events

System Organ Class Preferred Term	EB-101-Phase 1/2a ^[1] (N=7)	EB-101-CL-301^[2] (N=11)	Total (N=18)
All SAE	5 (71.4)	6 (54.5)	11 (61.1)
Blood and lymphatic system disorders	2 (28.6)	0	2 (11.1)
Anemia	2 (28.6)	0	2 (11.1)
Gastrointestinal Disorders	0 (0.0)	1 (9.1)	1 (5.6)
Ascites	0 (0.0)	1 (9.1)	1 (5.6)
Infections and infestations	3 (42.9)	1 (9.1)	6 (33.3)
Cellulitis	2 (28.6)	0	2 (11.1)
Enterocolitis infectious	1 (14.3)	0	1 (5.6)
Wound infection	0	1 (9.1)	1 (5.6)
Metabolism and nutrition disorders	2 (28.6)	0	2 (11.1)
Failure to thrive	1 (14.3)	0	1 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (28.6)	1 (9.1)	3 (16.7)
Metastatic squamous cell carcinoma	1 (14.3)	0	1 (5.6)
Intraductal Proliferative Breast Lesion	0 (0.0)	1 (9.1)	1 (5.6)
Squamous cell carcinoma	2 (28.6)	1 (9.1)	3 (16.7)
Squamous cell carcinoma of skin	0	1 (9.1)	1 (5.6)
Reproductive system and breast disorders	1 (14.3)	0	1 (5.6)
Menorrhagia	1 (14.3)	0	1 (5.6)
Surgical and medical procedures	0	1 (9.1)	1 (5.6)
Toe amputation	0	1 (9.1)	1 (5.6)
Vascular Disorders	0 (0.0)	1 (9.1)	1 (5.6)
Vena Cava Thrombosis	0 (0.0)	1 (9.1)	1 (5.6)

Source: Reviewer adapted from 120 safety update report, Table 14: Pages: 30-31. Data cutoff date: 16 October 2023

¹N corresponds to Phase 1/2a patients (including data collected during Phase 1/2a LTFU and EB-101-LT-001).

²N corresponds to Phase 3 patients including data collected during EB-101-LT-001

8.4.3 Study Dropouts/Discontinuations

Fifteen subjects were into Study EB-101-LT-001 (10 from Study EB-101-CL-301 and 5 from Study 14563/31095 EB-101). Of note, 5 of the 7 patients in Study 14563/31095 EB-101 were enrolled in the current study [Study EB-101-LT-001] because 2 patients died in the follow-up of Study 31095 EB-101. No deaths were reported in Study EB-101-CL-301 and all eligible subjects enrolled into the EB-101-LT-001 study. At the time of data analysis for the summary of clinical safety 120-Day safety update, 1 subject from EB-101-CL-301 enrolled into study for a total of 16 subjects enrolled. However, another subject later withdrew because they were lost to follow-up. In total 15 subjects were evaluated for the LTFU study and 120-day safety update.

8.4.4 Common Adverse Events

The AEs with a cumulative incidence of $\geq 10\%$ were procedural pain, local reaction, wound infection, pruritis, muscle spasm, elevation of blood immunoglobulin A and G.

Reviewer comment:

- The elevation of blood immunoglobulin A and G occurred in one subject each. Because there was no reported laboratory baseline and no clinical manifestation of the laboratory abnormality, the clinical significance remains unclear.*

The most frequent adverse reactions (incidence $\geq 10\%$) summarized in Table 30.

Table 30: Adverse Reactions (Incidence $\geq 10\%$) Following Treatment With EB-101

Adverse Reactions	Subjects n (%), (N=18) ^a
Any adverse reaction	10 (55.6)
Local reaction	3 (16.7)
Procedural pain	7 (38.9)
Pruritis	2 (11.1)
Wound infection	3 (16.7)

Source: The reviewer adapted from Summary of Clinical Safety 120-Day safety update. Table: 7.3.5, pages: 1-6.

^a Corresponds to Phase 1/2a & Phase 3 Pooled including data collected during Phase 1/2a LTFU and EB-101-LT-001.

Reviewer comment:

- Local reaction refers to an immune reaction which occurred within EB-101 wounds. Notably all local reactions only identified in the Phase 1/2a (14593/31095) study. Perhaps components which were removed from the final drug product after the Phase 1/2a study can explain the higher incidence of local reactions.*
- Due to the small number of subjects enrolled in the studies for EB-101, and the frequency of single AEs, a 10% incidence rate was chosen to accurately capture commonly occurring AEs with EB-101.*

8.4.5 Clinical Test Results

There were multiple hematologic and chemistry parameter abnormalities at baseline for many subjects. The most frequently occurring laboratory abnormalities were low hemoglobin, elevated C-reactive protein (CRP) and elevated platelets. These abnormalities persisted throughout the studies without clinical significance. There were 10 TEAEs of anemia 2 moderate, 6 severe and 2 life-threatening or debilitating. All serious TEAEs of anemia were assessed as unrelated to EB-101.

RCR testing was conducted at baseline and throughout the study. There were no positive RCR results observed pre-treatment or post grafting. There were no clinically significant vital signs or physical examination findings

8.6 Safety Conclusions

The clinical program included 3 studies (14563/31095 EB-101 (N=7), EB-101-CL301 (N=11) and EB-101-LT-001 (N=15)) for this BLA review. Ninety-nine wounds 18 subjects were treated. There was a total of 230 TEAEs reported. There were 6 TEAEs in 9

subjects assessed as related to EB-101. Nine subjects experience 29 serious TEAEs, none of which were related to EB-101. There were 2 deaths that were assessed as unrelated to EB-101. There were no serious TEAEs related to EB-101 or TEAEs leading to treatment discontinuation in this study.

Forty-seven TEWAEs were reported in 33 wounds of which 15 TEWAEs in 14 wounds were related to EB-101. There were no serious TEWAEs, TEWAEs leading to treatment discontinuation, or TEWAEs leading to death.

There were no clinically significant vital signs or physical examination findings reported during the studies.

The combined safety analysis of these studies shows that EB-101 treatment in this population is well tolerated with a favorable benefit/risk profile.

Reviewer Comment:

- RDEB disease is rare and life-threatening with a high risk for the development of SCC, therefore surveillance for emergence of SCCs in wounds treated with EB-101 were undertaken during the study. Two subjects developed SCC with regional metastasis that were not biopsied, because the protocols did not include biopsy of non-EB-101 treated wounds. Coupled with EB-101's integrating viral construct and a theoretical concern for insertional oncogenesis, it is unknown if these subjects' metastasis were due to exposure to EB-101, or due to disease progression. To address this concern, the review team recommended inclusion of evaluations for all cutaneous and non-cutaneous carcinomas for proviral DNA in the sponsor's proposed post marketing study registry.*

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with EB-101 application in pregnant women to inform a drug-associated risk. Animal developmental and reproductive toxicity studies were not conducted with EB-101.

One subject's partner became pregnant during the EB-101-CL-301 study. There were no maternal complications reported during the pregnancy or childbirth. The pregnancy resulted in a 37-week gestation birth with no congenital anomalies or post-natal period issues.

Reviewer's Comment:

- EB-101 is a localized treatment and laboratory testing demonstrated no evidence of systemic involvement. The pregnant subject did not receive EB-101.*

9.1.2 Use During Lactation

There is no information available on the presence of EB-101 in human milk, the effects on the breastfed infant, or the effects on milk production. Animal lactation studies have not been conducted with EB-101.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of EB-101 was studied in pediatric subjects. The safety and efficacy findings of EB-101 in pediatric subjects were similar to safety and efficacy findings in adult patients. EB-101 is not subject to PREA, since the product received Orphan Drug designation.

9.1.4 Immunocompromised Patients

The safety and effectiveness of EB-101 in immunocompromised patients was not studied.

9.1.5 Geriatric Use

Clinical studies did not include geriatric patients aged 65 years and over.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. CONCLUSIONS

EB-101 demonstrated substantial evidence of effectiveness for the treatment of large, chronic wounds in pediatric and adult subjects with RDEB, based on an adequate and well controlled Phase 3 study in addition to confirmatory evidence of safety and efficacy data demonstrated in the Phase 1/2a study.

The safety data from the review of these studies did not warrant a Risk Evaluation and Mitigation Strategies. However, the concern for insertional oncogenesis due to integrating nature of the viral vector construct of EB-101 has led to the requirement of a post marketing study. The sponsor initially proposed and has committed to conducting a long-term safety follow-up registry for EB-101 treated RDEB subjects in the post marketing setting.

In summary, EB-101 demonstrated a favorable benefit/risk profile for the treatment of chronic, large wounds in pediatric and adult subjects with RDEB, with mutation(s) in the *COL7A1* gene.

11. BENEFIT-RISK ASSESSMENT

11.1 Benefit-Risk Framework

Table 31. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions
Analysis of Condition	RDEB is a recessively inherited disorder characterized by skin fragility. RDEB is caused by mutations in the <i>COL7A1</i> gene resulting in reduction of collagen type VII (C7), a main component of anchoring fibrils (AF) necessary to maintain epidermal-dermal cohesion. The estimated incidence is 0.2–6.65 per million births with a prevalence of 3.5–20.4/million people. It may be present in the neonatal period and manifests blistering and erosions affecting the whole body. RDEB is a painful condition with secondary infections and malignant complications leading to death. Life expectancy is around 30 years with a median survival after a first squamous cell carcinoma (SCC) diagnosis of 2.4 years.	RDEB is a rare, life-threatening disease, with serious manifestations beginning in childhood. It causes considerable morbidity and reduced life expectancy.
Current treatment options	There are two FDA approved products for the treatment of RDEB: VYJUVEK® (beremagene geperpavec-svdt), a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy indicated for the treatment of wounds in patients six months of age and older with DEB and FILSUVEZ (birch triterpenes), a botanical drug product, indicated for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in adult and pediatric patients 6 months of age and older.	VYJUVEK and FILSUVEZ require routine application until the wound is healed. Need for constant (weekly or daily) application may lead to poor compliance. Additional therapies in this serious disease will help provide an additional treatment option and may help address cases where the available products are either not effective or not well tolerated.
Benefit	<p>The primary evidence of EB-101's efficacy is based on improvement of ≥50% wound healing from Baseline and pain reduction at 6 months post treatment, which was observed in a multicenter, randomized, inpatient-controlled study in aged ≥6 years RDEB subjects.</p> <p><u>Efficacy:</u> co-primary endpoints of wound healing and patient reported outcome of pain reduction associated with treatment of RDEB were assessed at Week 24 with 81.4% of treated wounds achieving ≥50% healing from baseline compared to control wounds with 16.3%; $P<0.0001$. The mean pain reduction in the treated group was 3.07 points on the Wong-Baker FACES pain scale at 24 weeks, compared to 0.90 in the control group ($P=0.0002$). The rate of complete wound healing from baseline at Week 24, assessed as secondary endpoint, was 16.3% in the treated group, compared to control of 0%. $P=0.0160$).</p>	<p>The Phase 3 study was an adequate and well controlled study and provides evidence of effectiveness. One-time application of EB-101 to RDEB wounds was effective in partial and/or complete healing of wounds due to RDEB.</p> <p>In Phase 1/2a study (41563/31095) and overall LTFU studies (EB-101-LT-001), multi-year improvements were noted in wound healing and pain reduction providing evidence for durability of the EB-101 effect on treated wounds.</p>

Dimension	Evidence and Uncertainties	Conclusions
Risk	The risks of EB-101 were characterized in 18 subjects treated across the Phase 3 and Phase 1/2a studies. The most common risks observed were wound infection, local reaction, pruritis and procedural pain.	The rarity and severity of RDEB resulted in a small but adequate safety database for assessing the risk of the EB-101 in this population.
Risk Management	<p>The risk management plan for EB-101 includes:</p> <p>A 15-year LTFU study for subjects treated with EB-101</p> <p>A PMR which includes conducting a LTFU safety registry study for EB-101 treated subjects for assessment of development both cutaneous and non-cutaneous carcinomas in non-EB-101 treated sites.</p>	Both the ongoing LTFU and the planned PMR LTFU safety registry study is adequate for continuous safety monitoring of EB-101 in the RDEB treated population for 15 years. Safety monitoring will include visits with wound examination, wound-healing durability, review of AEs and SAEs, evaluations for malignancies and potential retroviral infection, and changes to concomitant medications and procedures.

11.2 Benefit-Risk Summary

The overall benefit/risk is favorable for the one-time application of EB-101 to wounds for pediatric and adult subjects with RDEB with mutation in the *COL7A1* gene.

EB-101 demonstrated substantial evidence of effectiveness in achieving $\geq 50\%$ healing of wounds from Baseline and pain reduction in RDEB subjects based on the primary evidence of effectiveness from the adequate and well-controlled Phase 3 study supported by additional safety and efficacy demonstrated in the Phase 1/2a study.

The risks of EB-101 are characterized based on the safety database of 18 subjects in the Phase 3 and Phase 1/2a study. Because RDEB is a rare and serious disease, the small safety database is acceptable.

The safety profile of 2 subjects with ages 6 and 16 years in Phase 3 supports the safety of EB-101 in pediatric subjects.

The risks of EB-101 will be further characterized with an ongoing 15-year LTFU safety study and proposed long-term safety follow-up registry for EB-101 treated RDEB subjects in the post marketing setting, coupled with suitable prescribing information.

11.3 Recommendations on Regulatory Action

The Applicant has provided substantial evidence of effectiveness for EB-101 in pediatric and adult patients with RDEB based on a single adequate and well controlled randomized, phase 3 study accompanied by confirmatory evidence from the mechanism of action of the product in addition to supportive efficacy data from an early, exploratory study. The studied population included adults and pediatric patients 6 years old and older. RDEB is a monogenic disease and the disease pathophysiology/progression and response to treatment is expected to be similar across RDEB patients of different ages. Therefore, it is scientifically reasonable to extrapolate efficacy and safety from older pediatric patients and adults to younger pediatric patients (younger than 6 years of age).

Based on our clinical evaluation, the demonstrated benefits of EB-101 outweigh the observed risks and the benefit-risk assessment is favorable. The review team recommends approval of EB-101 for the treatment of wounds in adult and pediatric patients with RDEB.

11.4 Labeling Review and Recommendations

Several revisions were made to the Applicant's proposed United States Prescribing Information. Please see Table 32 below for a summary of significant changes to the United States Prescribing Information.

Table 32: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	For the treatment of wounds associated with recessive dystrophic epidermolysis bullosa (RDEB).	Revised to specify indicated population: For the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB).
Section 2: Dosage and Administration	-	Section 2.1: Revised to include dosage information and coverage area for each EB-101 sheet. Section 2.2: Revised to include subheadings of receipt and storage, preparation, and administration. Information was reorganized using bullets to improve readability.
Section 5: Warnings and Precautions	RVV-Mediated Insertional Oncogenesis Transmission of Infectious Agents	Subsection on RVV-Mediated Insertional Oncogenesis was added due to the potential integration of retroviral vector genes which may lead to oncogenic transformation. Subsection on transmission of infectious agents was added as the product is manufactured using human and bovine-derived reagents.
Section 6 Adverse Reactions (Safety)		The information in this section was revised to include 1) brief description of safety database 2) removed study description and population characteristics added a cross-reference to section 14 where these details are provided 3) include data from Phase 3 study only as other studies do not provide any additional clinically meaningful safety information.
Section 8: Use in Specific Population Section 14: Clinical Studies Section 17: Patient Counseling Information	Section 8.4 Pediatric Use	This section was revised to specify the pediatric population included in the pivotal study and appropriate cross-references. This section was revised to include data only from the Phase 3 study which provided the substantial evidence of efficacy for EB-101. This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).

Source: Created by FDA Associate Director of Labeling
Abbreviations:

11.5 Recommendations on Post marketing Actions

The safety data from the review of these studies did not warrant a Risk Evaluation and Mitigation Strategies. However, the concern for insertional oncogenesis due to integrating nature of the viral vector construct of EB-101 has led to the requirement of a post marketing study. The sponsor initially proposed and has committed to conducting a long-term safety follow-up registry for EB-101 treated RDEB subjects in the post marketing setting

APPENDICES:

Appendix 1: (b) (4), (b) (6) detail of disclosable financial interest/arrangement

EXHIBIT A FORM OF STATEMENT OF WORK

The Statement of Work should address the following items:

- Description of Services
 - Pre meeting survey
 - Advisory Board Meeting

Fixed Fee. Consultant shall perform all Services for the fixed fee of U.S. (b) (4), (b) (6) (b) (4), (b) (6) Abeona shall have no obligation for payments in excess of such amount unless a higher amount is authorized by Abeona in advance in writing. Consultant shall invoice Abeona on the schedule set forth in the Statement of Work, and Abeona's payments shall be due in accordance with the Agreement. In the event that the Parties agree that changes in the Services to be performed hereunder are advisable because of results observed, or because of either Party's request, and if such changes result in increased or decreased costs for Consultant, then the Parties shall negotiate in good faith and agree in writing on an equitable increase or decrease, as applicable, to the fixed fee.

Travel and Expenses. Abeona will reimburse all reasonable expenses associated with Consultant's provision of services under this agreement in accordance with all applicable Company travel and expense reimbursement guidelines.

Appendix 2: Potential Bias for sub-investigator: (b) (4), (b) (6)

(b) (4), (b) (6) who received payment for participating in an advisory board meeting in 2019, prior to the start of the VIITAL study.

(b) (4), (b) (6) a sub-investigator in the study, had a role that inherently minimized bias in the study in several ways. He did not participate in the design of the study, selection of endpoints, nor the statistical analysis plan. (b) (4), (b) (6) is a plastic surgeon whose sole purpose as sub-investigator in the study was to complete the surgical application of pz-cel sheets based on instruction from the Principal Investigator, Dr. Jean Tang. Dr. Tang selected the wounds for randomization prior to meeting with the surgical team, thus creating a firewall between wound selection for randomization and (b) (4), (b) (6) In other words, (b) (4), (b) (6) was a resource to Dr. Tang to carry out pz-cel placement and suturing

on to study wounds. Additional important steps taken that minimized potential bias were rooted in the division of the teams and responsibilities. (b) (4), (b) (6) did not collect any of the study data, nor did he perform any of the endpoint assessments in the study. He is a member of the (b) (4)

(b) (4) and not part of the Clinical Trial Research Unit (CTRU) nor the research office responsible for the study. Furthermore, the study was conducted under the oversight of an Institutional Review Board (IRB), ensuring compliance with ethical guidelines and impartiality in trial execution. Moreover, Dr. Tang documented her assessment of study wounds using wound photos she took and collected at baseline and at all study visits, which were reviewed and collected in their entirety during the FDA's BIMO inspection at Stanford with no findings. These photos were included in the clinical study report (CSR) for the study.