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| Application Type | Original BLA |
| STN | 125807/0 |
| CBER Received Date | September 25, 2023 |
| PDUFA Goal Date | April 29, 2025 |
| Division / Office | OTP/OCE/DCEGM/GMB4 |
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| Applicant | Abeona Therapeutics Inc. |
| Established Name | Prademagene zamikeracel |
| (Proposed) Trade Name | ZEVASKYN |
| Pharmacologic Class | Subject's own cells that have been genetically modified via retroviral transduction to express the COL7A1 gene. |
| Formulation(s), including Adjuvants, etc | Epidermal sheets each measuring approximately 40cm ² (5.5 cm x 7.5 cm) and consisting of patient's own, viable, gene-corrected keratinocyte cells that contain functional copies of the COL7A1 gene, which express collagen 7 (C7) protein. |
| Dosage Form(s) and Route(s) of Administration | ZEVASKYN is composed of autologous keratinocyte cells that contain functional copies of the COL7A1 gene and are produced from subjects that have mutations in their C7 collagen-producing gene. ZEVASKYN is an autologous therapy for topical application only. |
| Dosing Regimen | The number of sheets to use is determined by the availability of ZEVASKYN sheets and at the discretion of the treating physician |
| Indication(s) and Intended Population(s) | Treatment of wounds associated with recessive dystrophic epidermolysis bullosa (RDEB) |

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GLOSSARY

| | |
|--------------|---|
| BLA | Biologics license application |
| C7 | Type 7 collagen |
| Cm | Centimetre |
| CMC | Chemistry, manufacturing and controls |
| FDA | Food and Drug Administration |
| IGA | Investigator's Global Assessment |
| LEAES | Autologous skin grafts transduced with a retroviral vector containing the gene encoding type VII collagen |
| LOCF | Last observation carried forward |
| (b) (4) | (b) (4) |
| LTFU | Long-term follow up |
| LZRSE-Col7A1 | LZRSE containing full length human COL7A1 gene |
| NC1 | Non-collagenous region 1 of the collagen 7 molecule |
| PI | Principal investigator |
| PZ | Prademagene zamikeracel |
| QOLEB | Quality of Life in Epidermolysis Bullosa |
| RCR | Replication-competent retrovirus |
| RDEB | Recessive dystrophic epidermolysis bullosa |
| SAE | Serious adverse event |
| SCC | Squamous cell carcinoma |
| SD | Standard deviation |
| SOC | Standard of care |
| TEAE | Treatment emergent adverse event |
| US | United States |
| USA | United States of America |
| WRO | Written response only |
| ZBI-12 | Zarit Burden Interview Short Form |
| SAP | Statistical analysis plan |
| IR | Information request |

1. EXECUTIVE SUMMARY

EB-101, under the trade name of ZEVASKYN, is composed of primary autologous keratinocytes from subjects with recessive dystrophic epidermolysis bullosa (RDEB) that have been transduced ex vivo with a Moloney leukemia virus-derived retroviral vector (LZRSE) containing full-length human *COL7A1* gene to form gene-corrected epidermal sheets with normal type 7 collagen (C7) expression. Abeona Therapeutics Inc. submitted the complete results from the pivotal study EB-101-CL-301 (VITAL) in this Biologics License Application (BLA) to support the indication of treatment of wounds associated with RDEB.

Study EB-101-CL-301 was a multicenter, randomized, intra-subject controlled, Phase 3 study comparing surgical application of EB-101 with standard of care (SOC) for the treatment of large, chronic wounds in subjects with RDEB. A total of 11 subjects with 43 matched wound pairs were randomized to receive EB-101 or SOC. All randomized subjects completed the study. The study had two co-primary efficacy endpoints. The first co-primary endpoint was the proportion of randomized wound pairs with $\geq 50\%$ healing from Baseline at Week 24 (Month 6) as determined by principal investigator (PI) and confirmed at Week 26. The response rate for the wounds treated with EB-101 was 81.4% (35 out of 43) compared to 16.3% (7 out of 43) for the wounds treated with SOC. This endpoint was statistically significant with a p-value of <0.0001 . The second co-primary efficacy endpoint was pain reduction at Week 24 from baseline, assessed by the Wong-Baker FACES Scale. The pain reduction from baseline for wounds treated with EB-101 was 3.07 (standard deviation (SD)=3.188), compared to 0.90 (SD=2.730) for wound treated with SOC. The pairwise difference in pain reduction was statistically significant with a p-value of 0.0002.

The key secondary endpoints were proportion of randomized wounds with complete wound healing from Baseline at Week 12 (Month 3) and Week 24 (Month 6). Among the wounds treated with EB-101, 14% (6 out of 43) and 16.3% (7 out of 43) of the wounds were completely healed at Week 12 and Week 24, respectively. Among the wounds treated with SOC, none was completely healed at Week 12 and Week 24. Both key secondary endpoints were statistically significant ($p=0.0316$ for Week 12 and 0.0160 for Week 24).

No deaths were reported during the study. Four treatment emergent adverse events (TEAEs) in 4 subjects were related to EB-101: 2 TEAEs of procedural pain in 2 subjects and 1 TEAE each of muscle spasms and pruritus in 1 subject.

I have verified the primary and key secondary efficacy analysis results. Based on the available data from Study EB-101-CL-301, the statistical evidence supports approval of EB-101 for treatment of wounds associated with RDEB.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

RDEB is an ultra-rare, severe inherited connective tissue disorder caused by the absence of C7. In the United States (US), there is an estimated prevalence of 1.35 per one million. RDEB is often caused by bi-allelic loss of function mutations in the gene *COL7A1*, which encodes C7. Mutations in *COL7A1* lead to disruption in keratinocyte adhesion, reducing mucocutaneous mechanical stability of stratified squamous and corneal epithelium and resulting in painful blistering of the uppermost dermis and mechanical fragility. Lack of C7 causes a delay in cutaneous wound healing, increased risk of infection, inflammation, and development of large, severely painful, open wounds from minor trauma to skin. Overall, 50% of subjects with RDEB die before 35 years of age and 75% die before 40 years of age. Aggressive squamous cell carcinoma (SCC) is the most common cause of death in subjects with RDEB.

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

There is no approved treatment for RDEB. Management of subjects with RDEB is presently limited to wound care and attempts to minimize trauma.

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

A Phase 1/2a open-label, single center long-term study evaluating the safety and efficacy of EB-101 (Study 14563/LTFU Study 31095) was conducted in a total of 7 subjects (ages 18-45). In this study, 38 chronic wounds and 4 induced wounds were treated with EB-101. During the 8 years of follow-up (mean 5.9 years, range 4-8 years), some efficacy data on durability of efficacy was collected.

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

Regulatory history with statistical implications is summarized below:

- On December 16, 2022, a Type B written response only (WRO) was submitted to obtain written feedback from Food and Drug Administration (FDA) on various elements of the clinical, nonclinical and chemistry, manufacturing, and control (CMC) development plan to support a prademagene zamikeracel (PZ) BLA submission in the second quarter of 2023 for treatment of wounds associated with RDEB.
- On January 27, 2023, a WRO to the Type B Pre-BLA Meeting was provided to Abeona Therapeutics, Inc. In this written response, FDA had two statistical comments for the sponsor:
 - Request for clarification how the sponsor proposes to permute under null hypothesis when conducting the re-randomization test and submission of the analysis program for review.

- Clarification on what the sponsor meant by “if there is no intra-pair correlation” when discussing the analysis of the first co-primary endpoint.

The sponsor provided their responses on February 15, 2023. The FDA determined that the responses were adequate.

- On July 25, 2023, the sponsor submitted a meeting request to discuss FDA’s feedback on various element of the clinical and CMC development plan to support a BLA submission. In this meeting package, the sponsor proposed to pool the efficacy data from Phase 1/2a Study (Study 14563) and its long-term follow-up (LTFU) study (Study 31095), the Phase 3 Study (VIITAL study), and the global LTFU study (Study EB-101-LT-001) to support efficacy. FDA advised that it is not likely to be helpful to conduct pooled analyses of efficacy data from the different studies due to the differences in major design elements (e.g., lack of randomized controlled wounds and differences in efficacy assessment in the Phase 1/2 study) between the studies. FDA requested the sponsor to submit separate efficacy analysis for Phase 1/2a study and Phase 3 studies, respectively.
- On March 4, 2024, an information request (IR) was sent to provide all the prior versions of the statistical analysis plan (SAP) and prior statistical communications in regard to the trial EB-101-CL-301. The response to this IR was received on March 14, 2024. The responses were adequate.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a statistical review without unreasonable difficulty.

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

5.1 Review Strategy

This memo reviews the efficacy and safety results of the pivotal study EB-101-CL-301 for the indication of treatment of wounds associated with RDEB.

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

The review memo was based on the draft labeling (module 1.14.1); the protocol and its amendments (module 5.3.5.1), the clinical trial report (module 5.3.5.1), the SAP (module 5.3.5.1), clinical trial efficacy report (module 2.7.3), the data files (module 5.3.5.1) for Study EB-101-CL-301 submitted on STN 125807/0. In

addition, all prior versions of the SAP (module 5.3.5.1) for Study EB-101-CL-301 submitted on STN 125807/36 were reviewed.

5.3 Table of Studies/Clinical Trials

Table 1: Overview of Clinical Trials

| Study Name | Trial design | Number of Subjects | Dosing regimen | Study Objectives |
|--|---|---|--|---|
| EB-101-CL-301 (Phase 3) | Phase 3, multicenter, randomized, intra-patient-controlled study for the treatment of RDEB subjects with large, chronic wounds (≥ 6 years old) | Screened: 15 Enrolled: 11 | Typically 40 centimetre ² (cm ²) keratinocyte sheets for surgical application to cover wounds | Evaluate the efficacy and safety of EB-101 for the treatment of RDEB patients with large, chronic wounds |
| 14563/Long-term follow up (LTFU) Study 31095 | Phase 1/2a, open-label, single-center long-term safety and efficacy study (≥ 13 years old) | Screened: 10 Enrolled: 7 | Typically 40 cm ² keratinocyte sheets for surgical application to cover wounds | Evaluate the wound healing of autologous skin grafts transduced with a retroviral vector containing the gene encoding type VII collagen (LEAES) in subjects with RDEB and to evaluate the safety of LEAES, and the long-term safety of subjects with RDEB who have been treated with autologous skin grafts transduced with LEAES |
| EB-101-LT-001 | Non-interventional multicenter long-term follow-up safety and efficacy study | From Phase 1/2a: 5 From Phase 3: 10 Total: 15 | N/A | Evaluate the long-term efficacy and safety of EB-101 in subjects who participated in a previous clinical trial and received EB-101 treatment for RDEB. |
| EB-101-CL-301 (Phase 3b) | A multicenter, open-label, single-arm phase 3b safety study of one-time surgical application of up to 8 EB-101 for the treatment of large, chronic RDEB wounds in each of approximately 10-12 subjects. All subjects will be followed through 24 weeks post-treatment | Screened: 4 Enrolled: 3 | Typically 40 cm ² keratinocyte sheets for surgical application to cover wounds | Evaluate and further characterize the safety of EB-101 for the treatment of large, chronic RDEB wounds in new and previously EB-101 treated subjects 6 years and older, and support manufacturing requirement by providing a set of biopsies from each subject, which may be used to support assay development, process development, and process/product optimization activities. |

Source: BLA 125807/0 (Module 5.2) Tabular Listing of Clinical Studies.pdf, page 1-6

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study EB-101-CL-301

Study EB-101-CL-301 was titled “VITAL: A Phase 3 study of EB-101 for the treatment of recessive dystrophic epidermolysis bullosa (RDEB)”.

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective:

- Evaluate the efficacy and safety of EB-101 for the treatment of RDEB subjects, with large, chronic wounds.

6.1.2 Design Overview

EB-101-CL-301 (VITAL) was 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 subjects with RDEB. This study of one-time surgical application of approximately 36 autologous, gene-corrected keratinocyte sheets (EB-101 sheets) for the treatment of eligible RDEB wound sites in comparison with matched paired untreated wound sites was expected to enroll approximately 10 to 15 subjects. Within each subject, matched wound pairs were randomized in a 1:1 ratio to EB-101 versus SOC.

6.1.3 Population

Key inclusion criteria:

1. Clinical diagnosis of RDEB
2. Age 6 years or older, willing and able to give consent/assent; if under the age of 18 years, guardian(s) is/are willing and able to give consent
3. Positive expression non-collagenous region 1 of the collagen 7 molecule (NC1)+ in the skin
4. Two confirmed RDEB C7 mutations with recessive inheritance patterns (or confirmation that parents don't have any evidence of dominant disease)
5. At least 40 cm² areas of chronically wounded areas on the trunk and/or extremities suitable for EB-101 application (open erosions)
6. Able to undergo adequate anesthesia to allow EB-101 application procedure to take place
7. Must have a least two matched eligible wound sites (1 pair) that meets all the following criteria:
 - An area ≥ 20 cm²
 - Present for ≥ 6 months
 - Stage 2 wound defined as an open skin wound with partial thickness loss of dermis that has not extended through the dermis into subcutaneous tissue
8. All women of childbearing potential must have a negative urine pregnancy test and use a reliable birth control method throughout the duration of the study and for 6 months post treatment

9. Must be on stable pain medication regimen at least 30 days prior to Screening

6.1.4 Study Treatments or Agents Mandated by the Protocol

EB-101 is composed of primary autologous keratinocytes from subjects with RDEB that have been transduced ex vivo with a Moloney leukemia virus derived retroviral vector (LZRSE) containing full length human COL7A1 gene (LZRSE-Col7A1) to form gene-corrected epidermal sheets with normal C7 expression.

6.1.6 Sites and Centers

The study was conducted at 2 centers Stanford Medicine Outpatient Center (10 subjects) and Department of Dermatology, UMass Memorial Health Care (1 subject) in the United States of America (USA).

6.1.8 Endpoints and Criteria for Study Success

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

- Proportion of randomized wound pairs with healing $\geq 50\%$ from Baseline at Week 24 (Month 6) as determined by direct assessment of the Principal Investigator
- Pain reduction assessed by the mean differences in scores of the Wong-Baker FACES scale between randomized wound pairs at Week 24 (Month 6)

Secondary efficacy endpoints:

- 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 (Month 3) and Week 24 (Month 6) as determined by direct assessment of the Principal Investigator.

Criteria for study success:

Both co-primary endpoints were tested using a randomization test at a two-sided 5% level of significance. The study was considered a success if both primary efficacy endpoints were statistically significant in favor of EB-101 compared to SOC.

A pre-specified hierarchical testing strategy was utilized for secondary efficacy endpoints. Complete wound healing at Month 6 was tested first at a two-sided 5% significance level. If and only if this endpoint were met, the secondary endpoint of complete wound healing at Month 3 would be tested at two-sided 5% significance level.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypothesis:

Primary efficacy endpoint:

Null: There is no difference in the randomized wound pairs between the EB-101 treated and SOC treated wounds in the healing rates ($\geq 50\%$ healing improvement) at the end of 24 weeks (with a confirmation at least 2 weeks later) OR the mean wound pain reduction measured in Wong-Baker FACES Pain Scale at the end of 24 weeks

Alternative: The treated wounds have a higher healing rate than untreated wounds AND that the treated wounds have a higher mean in wound pain reduction than that in untreated wounds at the end of 24 weeks.

Secondary efficacy endpoint:

The following statistical hypotheses would be tested using hierarchical strategy in the following order,

1. Null: There is no difference in the randomized wound pairs between the EB-101 treated and SOC treated wounds in the complete healing rates at the end of 6 months
Alternative: The treated wounds have a higher completed healing rate than untreated wounds at 6 months
2. Null: There is no difference in the randomized wound pairs between the EB-101 treated and SOC treated wounds in the complete healing rates at the end of 3 months
Alternative: The treated wounds have a higher completed healing rate than untreated wounds at 3 months

Sample Size Estimation:

The power calculation of the first co-primary endpoint was based on the observed healing rates in the Phase 1/2a trial, in which 36 of 38 treated wounds and 0 of 6 untreated wounds achieved $\geq 50\%$ wound healing. The upper bound of 90% exact confidence interval for the untreated group (39%) and lower bound of 90% exact confidence interval for the treated group (84%) were used in the sample size calculation.

For the second co-primary endpoint, the Phase 1/2a trial's Week 24 pain assessment data were used. The proportions of pain reduction in treated and untreated wounds were assumed to be 84% and 50%, respectively, in the power calculation.

The power calculation also assumed that all subjects contributed the same number of wound pairs and that all wound pairs were independent. Table 2 shows the power for various sample sizes.

Table 2. Statistical Power for Given Number of Wound Pairs and Minimum Detectable Effect Size for Wound Pain Reduction

| # of Wound Pairs | 33 | 34 | 35 | 36 | 37 | 38 |
|---|-------|-------|-------|-------|-------|-------|
| Power for the 1 st Co-Primary Endpoint ($PP_{TT,H} = 84\%$ and $PP_{CC,H} = 39\%$) | 96% | 97% | 97% | 98% | 98% | 98% |
| Power for the Binarized 2 nd Co-Primary Endpoint ($PP_{TT,P} = 84\%$ and $PP_{CC,P} = 50\%$) | 82% | 83% | 84% | 85% | 86% | 87% |
| Power for the Study > (Row 1 x Row 2) | 79% | 81% | 82% | 83% | 85% | 86% |
| Minimum Detectable Effect Size for the 2 nd Co-Primary Endpoint | 0.730 | 0.728 | 0.727 | 0.727 | 0.727 | 0.727 |

Source: BLA 125807/0 (Module 5.3.5.1 EB-101-CL-301 – VITAL A Phase 3 Study of EB-101 for the treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB)) EB-101-CL-301 – SAP v7.0.pdf, Table 2, page 31 of 38

Analysis Population:

Intent-to-treat Population (ITT): All randomized pairs (i.e., EB-101-treated and SOC control) that were treated on Day 0. Day 0 as opposed to Day -1 was used for this population in case a randomized wound pair cannot be treated at Day 0.

Safety analysis Population (SA): All subjects with ≥ 1 wound that has been treated with EB-101.

Per-protocol Population (PP): All wounds in the ITT population excluding wound pairs with a protocol violation deemed major and warranted for exclusion.

Statistical Methods

Analysis of primary efficacy endpoints

Proportion of randomized pairs achieving $\geq 50\%$ healing at Week 24 and confirmed at 2 weeks later: If a wound site did not meet $\geq 50\%$ healing at the Week 24 and the Week 24+2 Week confirmation visit, the wound was considered not healed and recorded as 0. The healing rates for the treated and untreated wounds and the difference between them were calculated in a 2x2 table. For each randomized wound pair, the difference between EB-101 treated and SOC treated wound sites was calculated first. The difference was then averaged across all matched pairs within a study subject. The subject level average rate was then averaged across all study subjects in each arm.

Pain reduction at Week 24 from baseline: The pain reduction for each wound from baseline was calculated for each wound. A positive value represented a pain reduction (i.e., improvement) and a negative value represented pain worsening. The pairwise difference in the pain reduction value between matched treated wound and untreated wound was calculated. A positive paired reduction between treated and untreated wound indicates a larger pain reduction for the treated wound than the untreated wound. The pair difference in pain reduction was first averaged across all matched pairs within a subject. The subject level average values were then averaged across all study subjects in each arm.

Pain was assessed primarily via the Wong Baker FACES pain rating scale as defined in Protocol Version 6 (December 17, 2020) and beyond. In cases where the Wong Baker FACES pain rating scale was not done because the Numeric Rating Scale (NRS) was available prior to Protocol Version 6, the NRS pain results were used.

The significance of the observed difference (p-value) for both co-primary endpoints was calculated using a randomization test, according to a null distribution that was generated by permuting the treatment assignment of the observed data over all possible configurations. Here p-value is defined as the proportion of the absolute differences (2-sided) generated by permutations that equal or exceed the observed absolute difference. Each co-primary endpoint was tested using a randomization test and rejected at a two-sided 5% significance level.

Analyses of secondary endpoint:

The secondary endpoint of proportion of wound pairs with complete wound healing from Baseline in the intra-subject randomized wound pairs at Week 12 (Month 3) and Week 24 (Month 6): The same methods for the first co-primary endpoint of proportion of randomized pairs achieving $\geq 50\%$ healing at Week 24 and confirmed at 2 weeks later.

A pre-specified hierarchical testing strategy was utilized for the secondary endpoint testing whereby the secondary endpoint of complete wound healing was tested first at Month 6. If and only if complete wound healing at Month 6 meets statistical significance based on a two-sided 5% type I error rate, the secondary endpoint of complete wound healing at Month 3 was then tested at two-sided 5% significance level.

Handling Missing Data:

For the primary and secondary endpoint analysis, the last observation carried forward (LOCF) method was the primary method for dealing with missing data. Missing baseline values were not imputed in any situation.

Reviewer's comment: LOCF is generally not recommended as it makes strong assumption that the outcomes do not change after dropout and that dropout is not related to the treatment assigned. Sensitivity analyses using worst case scenarios (e.g. imputing the greatest observed pain reduction across all wounds to a control subject wound with missing baseline FACES pain score) were used. The overall conclusions remained the same.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 15 subjects were screened, 4 of whom were not eligible. The remaining 11 subjects were randomized and received treatment. All the randomized subjects completed the study. Forty-three randomized wounds in 11 subjects were treated with EB-101, and 43 randomized, paired control wounds were treated with SOC. Table 3 summarizes the analysis populations.

Table 3: Analysis Populations (Randomized and Received Treatment)

| | Randomized Wounds | | Non-Randomized Wounds |
|---------------------------------------|-------------------|----------------|-----------------------|
| Population, n (%) | Treated (N=43) | Control (N=43) | Treated (N=14) |
| Intention-to-Treat Population | 43 (50.0) | 43 (50.0) | -- |
| Wound Healing Per-Protocol Population | 38 (50.0) | 38 (50.0) | -- |
| Pain Per-Protocol Population | 42 (50.0) | 42 (50.0) | -- |
| Safety Analysis Population | 43 (43.0) | 43 (43.0) | 14 (14.0) |

Source: BLA 125807/0 (Module 5.3.5.1 EB-101-CL-301 – VITAL A Phase 3 Study of EB-101 for the treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB)) EB-101-CL-301 – Report Body.pdf, Table 9, page 62 of 131

6.1.10.1.1 Demographics

Table 4 provides a summary of the demographic and baseline characteristics. The mean age of the subjects enrolled was 22.5 with a range of 6 to 40 years. Seven of the eleven subjects were female and four were male. The mean age at diagnosis of RDEB was 63.9 months with a range of 0 to 372 months. Ten subjects were white, and one subject was of unknown race. Eight subjects were not Hispanic or Latino, two subjects were Hispanic or Latino, and one subject did not report his/her ethnicity. The mean number of wounds per subject was 9.1 with a range of 6 to 11. There were a total of 100 wounds among which 86

wounds were randomized and 14 wounds not randomized. The mean number of wounds randomized per subject was 7.81 with a range of 4 to 10. The mean height, weight and BMI were 159.01 cm, 48.27kg and 18.64 kg/m², respectively.

Table 4: Demographics and Baseline Characteristics

| Characteristics | Overall (N=11) |
|--------------------------------|-----------------------|
| Age at RDEB Diagnosis (months) | |
| n | 11 |
| Mean (SD) | 63.9 (123.14) |
| Median | 0.0 |
| Min, Max | 0, 372 |
| Age (years) | |
| n | 11 |
| Mean (SD) | 22.5 (9.10) |
| Median | 21.0 |
| Min, Max | 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) |
| Not Reported | 1 (9.1) |
| Height (cm) | |
| n | 11 |
| Mean (SD) | 159.01 (21.719) |
| Median (Min, Max) | 164.00 (101.6, 182.7) |
| Weight (kg) | |
| n | 11 |
| Mean (SD) | 48.27 (18.393) |
| Median (Min, Max) | 48.20 (12.1, 75.6) |
| BMI (kg/m2) | |
| n | 11 |
| Mean (SD) | 18.64 (6.387) |
| Median (Min, Max) | 16.90 (10.4, 33.4) |
| Number of Wounds | |
| n | 11 |
| Mean (SD) | 9.1 (1.64) |
| Median (Min, Max) | 10.0 (6, 11) |

n=number of observations; SD=Standard deviation; Min=Minimum; Max=Maximum, cm=Centimeter, kg=Kilogram, m=meter

Source: BLA 125807/0 (Module 5.3.5.1 EB-101-CL-301 – VITAL A Phase 3 Study of EB-101 for the treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB)) EB-101-CL-301 – Report Body.pdf, Table 10, page 63 of 131

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Among the 11 randomized subjects, 9 subjects had blood and lymphatic system disorders. Cardiac disorders were observed in 4 of the subjects. Congenital familial and genetic disorders were observed in 9 of the subjects. Ear and labyrinth disorders and endocrine disorders were observed in one subject. Three subjects had eye disorders.

6.1.10.1.3 Subject Disposition

All subjects who were randomized and treated completed the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

First co-primary endpoint: The proportion of randomized wound pairs with $\geq 50\%$ healing from Baseline at Week 24 (Month 6) as determined by the PI [to be confirmed at Week 26]. For the treated wounds, $\geq 50\%$ healing is observed in 81.4% (35 out of 43) compared to 16.3% (7 out of 43) in the control group. The difference in proportion of $\geq 50\%$ healing was found to be statistically significant in the study with a p value of <0.0001 .

Second co-primary endpoint: Pain reduction assessed by the mean differences in scores of the Wong-Baker FACES Scale between randomized wound pairs at Week 24 (Month 6). The mean pain reduction in the wounds treated with EB-101 was found to be 3.07 compared to 0.90 in the control group. The difference was found statistically significant with a p-value of 0.0002.

Table 5 summarizes the results for the two co-primary efficacy endpoints.

Table 5: Summary of the results for the co-primary efficacy endpoints.

| Primary efficacy endpoint | Treated (N=43) | Control (N=43) | P value |
|--|-------------------|-------------------|-----------|
| Proportion of randomized wound pairs healed from baseline at Week 24 | 35/43 (81.4%) | 7/43 (16.3%) | <0.0001 |
| Mean pain reduction from baseline at Week 24 | | | 0.0002 |
| n | 43 | 42 | |
| Mean (SD) | -3.07 (3.188) | -0.90 (2.730) | |

n=number of observations; SD=Standard deviation

Reviewer's comment: For the first primary efficacy endpoint, there were 8 wounds (4 controls and 4 treatment wounds) whose outcomes at Week 24 were imputed. All these wounds were found to have not healed more than $\geq 50\%$. There was no missing Week 26 assessment for wounds that were assessed at Week 24.

There was one control wound for which the baseline FACES pain score was missing. For the matched treated wound, the baseline FACES pain score was -4. The pain reduction from baseline at Week 24 for the control wound with missing baseline value was imputed with the highest pain reduction observed in the control wounds (-6) and the highest pain reduction observed in all wounds (-10). The results remained statistically significant.

Worst case imputation and complete case analysis provided p-value<0.00001. Therefore, using LOCF did not change the conclusion.

Additional sensitivity analysis was carried out for the first primary efficacy endpoint using a mixed effect logistic model with the dependent variable of wound healing status and treatment arm as covariate where subject ID and pair was considered as random effect. The result was consistent with the pre-specified primary efficacy endpoint analysis.

The subject-level results for the two co-primary efficacy endpoint is provided in Table 6. The proportion of randomized pairs from baseline healed at Week 24 was the same in Subject (b) (6). For all other subjects, the proportion of randomized pair healed in the treated group was larger than that in the control group. The mean pain reduction from baseline at Week 24 was the same in subject (b) (6). For most of the subjects the mean reduction in pain was higher in the treated group except for subjects (b) (6).

(b) (6)

Table 6: Summary of co-primary efficacy endpoints by subject

| Subject ID | Number of wound pairs | Proportion of randomized wound pairs from baseline healed at Week 24 | | Mean pain reduction from baseline at Week 24 | |
|------------|-----------------------|--|-------------|--|-------------------|
| | | Treated | Control | Treated Mean (SD) | Control Mean (SD) |
| (b) (6) | 4 | 0/4 (0.0%) | 0/4 (0.0%) | -1.50 (1.0) | -2.0 (0.0) |
| | 5 | 4/5 (80.0%) | 0/5 (0.0%) | 0.40 (0.89) | 0.40 (0.89) |
| | 3 | 3/3 (100.0%) | 0/3 (0.0%) | -8.57 (1.15) | -4.67 (1.15) |
| | 3 | 3/3 (100.0%) | 0/3 (0.0%) | -4.0 (2.0) | -2.67 (3.06) |
| | 4 | 4/4 (100.0%) | 1/4 (25.0%) | 0.0 (0.0) | -1.0 (1.15) |
| | 4 | 3/4 (75.0%) | 0/4 (0.0%) | -1.50 (1.0) | -2.00 (2.31) |
| | 5 | 3/5 (60.0%) | 1/5 (20.0%) | -5.20 (2.28) | -2.80 (1.79) |
| | 5 | 5/5 (100.0%) | 1/5 (20.0%) | -4.00 (0.0) | 1.50 (1.91)* |
| | 3 | 3/3 (100.0%) | 0/3 (0.0%) | -4.00 (3.46) | -0.67 (3.06) |
| | 5 | 5/5 (100.0%) | 3/5 (60.0%) | -5.60 (3.58) | 0.40 (1.67) |
| | 2 | 2/2 (100.0%) | 1/2 (50.0%) | 1.0 (1.41) | 5.0 (4.24) |

SD=Standard deviation

* Among 5 wounds in the control group, baseline value was missing for one of the wounds. Mean and SD was calculated based 4 wounds which had both baseline value and value at Week 24.

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%, $p=0.03$; Week 24: 16.3%, $p=0.02$) were observed to have completely healed at Weeks 12 and 24 from baseline compared with that of control wounds (0% at both time points).

6.1.11.3 Subpopulation Analyses

First Primary efficacy endpoint:

Table 7 summarizes the subgroup analyses for the first primary efficacy endpoint. A total of 36 wounds in 4 male subjects were randomized. At 24 weeks, 12 of the 18 wounds treated with EB-101 in male subjects healed more than 50%, compared to 1 out 18 wounds treated with SOC. A total of 50 wounds in the 7 female subjects were randomized. Among the EB-101 treated wounds, 23/25 wounds healed $\geq 50\%$, in contrast to 7/25 among the SOC treated wounds.

There were 5 subjects <21 years of age and 6 subjects who were ≥ 21 years of age. Among subjects <21 years of age, 18 wounds were randomized. For the EB-101 treated wounds, 13/18 were healed $\geq 50\%$, compared to 5/27 for the SOC treated wounds.

Ten of the 11 subjects enrolled were white, contributing a total of 80 wounds. The race of the remaining 1 subject was unknown. Subgroup analysis by race is not informative.

Table 7: Summary of first co-primary endpoint, wound healing $>50\%$, by sex, age and race

| | Number of subjects | Treated (N=43) | Control (N=43) |
|------------|--------------------|-------------------|-------------------|
| Sex | | | |
| Male | 4 | 12/18 (66.7%) | 1/18 (5.56%) |
| Female | 7 | 23/25 (92.0%) | 6/25 (24.0%) |
| Age, years | | | |
| <21 | 5 | 13/18 (72.2%) | 2/18 (11.1%) |
| ≥ 21 | 6 | 22/25 (88.0%) | 5/25 (20.0%) |

N=number of observations

Second Co-primary efficacy endpoint

Among the 18 EB-101 treated wounds in 4 male subjects, the mean pain reduction at Week 24 from baseline was -1.67. In contrast, for the 17 SOC treated wounds in 4 male subjects, the pain reduction at Week 24 from baseline was -0.471. Among the 25 EB-101 treated wounds in the 7 female subjects, the mean pain reduction from baseline at Week 24 was -4.08 compared to -1.20 for the SOC treated wounds.

The mean pain reduction for the EB-101 treated wounds in subjects aged <21 years was -0.78 compared to -0.11 for the SOC treated wounds. The mean pain

reduction for EB-101 treated wounds in subjects aged ≥ 21 was -4.72 compared to -1.50 for the SOC treated wounds. Table 8 summarizes the second co-primary endpoint by sex and age.

Table 8: Summary of second co-primary endpoint, FACES pain score, by sex and age

| | Treated | Control |
|------------------------|---------------|----------------|
| Sex | | |
| Male (4 subjects) | | |
| n | 18 | 17 |
| Mean (SD) | -1.67 (1.847) | -0.471 (2.065) |
| Female (7 subjects) | | |
| n | 25 | 25 |
| Mean (SD) | -4.08 (3.581) | -1.20 (3.109) |
| Age, years | | |
| <21 (5 subjects) | | |
| n | 18 | 18 |
| Mean (SD) | -0.78 (2.184) | -0.11(2.700) |
| ≥ 21 (6 subjects) | | |
| n | 25 | 24 |
| Mean (SD) | -4.72 (2.762) | -1.50 (2.719) |

n=number of observations; SD=Standard deviation

Due to small sample sizes and multiple comparisons, formal statistical comparisons were not made for the subgroup analyses. However, efficacy results were generally consistent across the subgroups.

6.1.11.4 Dropouts and/or Discontinuations

All subjects completed the study.

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Two (18.2%) subjects reported a total of 5 serious TEAEs. Out of these, 3 serious adverse event (SAE)s of wound infection were reported in 1 subject; and 1 SAE each of SCC of skin and toe amputation were reported in 1 subject.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The efficacy evaluation for treatment of wound associated with RDEB is based primarily on the pivotal study EB-101-CL-301.

EB-101-CL-301 was a multicenter, randomized, intra-subject controlled, Phase 3 study comparing surgical application of EB-101 with standard of care (SOC) for the treatment of large, chronic wounds in subjects with RDEB. A total of 11 subjects with 43 matched wound pairs were randomized to receive EB-101 or SOC. The study had two co-primary efficacy endpoints. The first co-primary endpoint was the proportion of randomized wound pairs with $\geq 50\%$ healing from Baseline at Week 24 as determined by principal investigator (PI) and confirmed at Week 26. The response rate for the wounds treated with EB-101 was 81.4% (35 out of 43) compared to 16.3% (7 out of 43) for the wounds treated with SOC. This endpoint was statistically significant with a p-value of <0.0001 . The second co-primary efficacy endpoint was pain reduction at Week 24 from baseline, assessed by the Wong-Baker FACES Scale. The pain reduction from baseline for wounds treated with EB-101 was 3.07 (SD=3.188), compared to 0.90 (SD=2.730) for wound treated with SOC. The pairwise difference in pain reduction was statistically significant with a p-value of 0.0002.

The key secondary endpoints were proportion of randomized wounds with complete wound healing from Baseline at Week 12 (Month 3) and Week 24 (Month 6). Among the wounds treated with EB-101, 14% (6 out of 43) and 16.3% (7 out of 43) of the wounds were completely healed at Week 12 and Week 24, respectively. Among the wounds treated with SOC, none was completely healed at Week 12 and Week 24. Both key secondary endpoints were statistically significant ($p=0.0316$ for Week 12 and 0.0160 for Week 24).

All randomized subjects completed the study. No deaths were reported during the study. Four treatment emergent adverse events (TEAEs) in 4 subjects were related to EB-101 (2 TEAEs of procedural pain in 2 subjects and 1 TEAE each of muscle spasms and pruritus in 1 subject).

10.2 Conclusions and Recommendations

The efficacy evaluation of EB-101 is primarily based on the data from a well-controlled Phase 3 multicenter, intra-subject controlled study in subjects with RDEB of age ≥ 6 years older where matched wound pairs were randomly assigned in a 1:1 ratio to receive EB-101 or SOC.

The co-primary and key secondary endpoints for the study were statistically met. Based on the available data from Study EB-101-CL-301, the statistical evidence supports approval of EB-101 for treatment of wounds associated with RDEB.