



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To:	Bao Nguyen, PhD Chair of the Review Committee Office of Therapeutic Products (OTP)
Through:	Kerry Welsh, MD, PhD Branch Chief, PB3
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Abeona Therapeutics
Product:	Zevaskyn (Prademagene zamikeracel)*
Application Type / Number	BLA / STN 125807
Proposed Indication	Treatment of wounds associated with recessive dystrophic epidermolysis bullosa (RDEB)
Submission Date:	September 25, 2023
Action Due Date:	May 24, 2024

* This product is also referred to as EB-101 throughout this memo.

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA STN 125807 based on the safety profile of Zevaskyn. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Zevaskyn, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Recessive dystrophic epidermolysis bullosa (RDEB) is an ultra-rare, life-threatening, autosomal recessive form of epidermolysis bullosa (EB) with symptoms present at birth, caused by the absence of type VII collagen protein. RDEB is characterized by mechanical fragility of the skin and other epithelial lined surfaces, resulting in painful chronic wounds, restrictive scarring, and aggressive squamous cell carcinoma. A modeling approach has estimated that there are approximately 3,850 patients in the US with RDEB. Currently, careful wound care with antibiotics, and opioid use for pain management has been the standard of care, though recently a non-integrating topical gene therapy (Vyjuvek) has been approved for the same indication. Vyjuvek is a topical gene therapy that requires weekly application of gel and wound healing is transient.

3 PRODUCT INFORMATION

3.1 Product Description

Zevaskyn is a topical, localized gene therapy in which a full-length collagen type VII alpha 1 chain (COL7A1) gene contained within a (b) (4) retroviral vector (LZRSE-Col7A1) is transduced ex vivo into a cell sheet isolated from previously obtained (b) (4) biopsies of the patient's own unwounded, unscarred skin. The COL7A1 gene is stably integrated into the genome of the patient's own keratinocytes and grafted onto the patient's skin as epidermal sheets. The retroviral vector is replication-incompetent.

Zevaskyn is typically provided as 40 cm² (5.5 × 7.5 cm²) cell sheets for surgical application to cover wounds. The sheets are surgically applied onto the patients' wounds in a healthcare setting. The number of sheets applied per treatment is determined by the availability of the Zevaskyn sheets and at the discretion of the treating physician.

The transportation media for Zevaskyn contains the following ingredients (b) (4)

The sheet also has a nylon suture, which functions as a visual indicator of the sheet's topography. Neither Zevaskyn sheets nor its excipients contain preservatives.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125807/0 is: Zevaskyn is a genetically engineered, autologous cell therapy indicated for the treatment of wounds associated with recessive dystrophic epidermolysis bullosa (RDEB).

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

This product has no prior approvals in any country.

5 DESCRIPTION OF PRADIMAGE ZAMIKERACEL (EB-101) CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed are from the Summary of Clinical Safety and individual study reports submitted to STN 125807/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125807/0 be approved. Please refer to the package insert for the final clinical safety data. The following studies form the safety analysis population:

Table 1. Summary of clinical studies supporting the safety of Zevaskyn

Study	N	Description
EB-101-CL-301	11	Interventional, multicenter, randomized, intra-patient controlled, Phase 3 study comparing EB-101 with standard of care for the treatment of large, chronic wounds in patients with RDEB. Pediatric (age 6 years or older) and adult patients were followed until Week 26.
14563/31095 EB-101	7	Interventional Phase 1/2a proof-of-concept, single-center, open-label, study to evaluate the efficacy and safety of EB-101 for 52 weeks in the treatment of adolescent (age 13 years or older) and adult patients. This is followed by a 5-year followup to the phase 1/2a study.
EB-101-LT-001	15	Ongoing non-interventional, multicenter, LTFU study in patients from 2 prior interventional studies (Study EB-101-CL-301 and Study 14563/31095 EB-101). Note that Study 14563 EB-101 had initial followup for up to five years in Study 31095 EB-101 and then is rolled into this long term study. Ten participants from EB-101-CL-301 and five participants from 14563/31095 EB-101 are being followed so far in this study.

*Adapted from Table 4, Clinical Overview, STN 125807, Module 2.5

Reviewer Comment: As RDEB is an ultra-rare condition, the small number of participants in the studies is expected.

5.2 Adverse events

5.2.1 Clinical study EB-101-CL-301

i) Most common AEs: A total of 62 treatment-emergent adverse events (TEAEs), defined as events which begin or worsen after the date of Zevaskyn application on any wound, were reported in all 11 patients. The most frequently reported TEAEs were thirteen TEAEs of wound infection in six patients, four TEAEs of procedural pain in four patients, and four TEAEs of constipation in three patients. Four nonserious TEAEs in four patients were considered related to Zevaskyn (procedural pain in two patients, muscle spasms in one patient, and pruritus in one patient).

Treatment-emergent wound adverse events (TEWAEs) were reported separately. There were 15 infections in the randomized treated wounds and four in the randomized control wounds, as well as three PTs of procedural pain in each group. Among non-randomized wounds, there were three PTs of procedural pain and six infections. Only the TEWAEs with PT procedural pain (randomized, treatment and control, and non-randomized) were considered related to Zevaskyn by the sponsor.

ii) SAEs: Five TEAEs in two patients were serious. One patient developed three SAEs of wound infection and a second patient developed squamous cell carcinoma of skin and a toe amputation. No serious AEs were considered to be related to treatment with Zevaskyn by the sponsor. No TEWAEs were serious.

iii) Deaths: There were no fatalities in this study.

iv) Adverse events of special interest (AESIs):

- a) Squamous cell carcinoma (SCC) --The SCC sample was tested and found negative for proviral genomic DNA. The blood sample for replication-competent retrovirus (RCR) could not be tested due to shipment delay.
- b) Localized/systemic immune response and Anti-C7 antibodies – All patient biopsies were negative for C7 immune complexes, as assessed by direct immunofluorescence. Serum IIF analysis of C7 expression was also negative for all patients assessed at screening.

Reviewer Comment: Since SCC associated with RDEB is both more frequent and more aggressive, and integrating gene therapy can lead to oncogenesis, a consistent testing algorithm will enable distinguishing disease-related malignancies from insertional oncogenesis related to treatment.

5.2.2 Clinical study EB-101-14563/31095

i) Most common AEs: A total of 121 treatment-emergent adverse events (TEAEs) were reported in all seven patients. The most frequently reported adverse events were: squamous cell carcinoma (16 events in two patients), wound infection (14 events in six patients), anemia (10 events in five patients), nausea (four events in four patients), and procedural pain (four events in four patients). Five patients had twelve TEAEs considered to be related to treatment: four procedural pain in four patients, three local reaction in one patient, two wound infection (non-study wounds) in two patients, and one patient with increased immunoglobulin G, immunoglobulin A, and pruritus.

Study wound AEs were summarized separately as TEWAEs. Among both treated chronic and treated induced wounds, TEWAEs included local reaction, wound infection, and pruritus. Twelve TEWAEs were reported in the eleven treated wounds. No TEWAEs were reported in control wounds. Eight TEWAEs were reported in chronic wounds and three in induced wounds. Nine were considered related to treatment by the Sponsor (five local reaction, two wound infection, and two pruritus).

ii) SAEs: Fourteen TEAEs were SAEs in four participants (four squamous cell carcinoma in two participants, three anemia in two participants, two failure to thrive in two participants, and one participant with metastatic SCC, cellulitis, enterocolitis infection, sepsis, and menorrhagia). These SAEs were not considered related to treatment with Zevaskyn by the sponsor.

iii) Deaths: Two participants experienced fatal TEAEs. One participant died of sepsis. The other participant died with failure to thrive, menorrhagia, cellulitis, anemia, and metastatic squamous cell carcinoma. These deaths were attributed to underlying disease and disease progression and considered unrelated to treatment by the sponsor.

iv) Adverse events of special interest (AESIs):

- a) Squamous cell carcinoma (SCC) – Two participants experienced multiple episodes of SCC. No SCC was located at treatment sites. All SCC that was tested for proviral genomic DNA was found to be negative. Blood RCR was negative.
- b) Localized/systemic immune response and Anti-C7 antibodies – Circulating anti-C7 antibodies were found in two patients and tissue-bound antibodies beyond trace staining were detected in four patients. These were transient or resolved by one year post-treatment without intervention. One patient was found to have pre-existing anti-C7 antibodies on a more sensitive test, though he had been initially tested negative on screening. This patient (described above as having died due to sepsis) died 5 years after treatment; however, the circulating antibodies were not thought to have contributed to his death, according to the sponsor, since he had no clinical signs of any severe systemic immune response.

***Reviewer Comment:** Since SCC is frequently managed as an outpatient, not all episodes of SCC are listed as SAEs. Though those biopsies of SCC that were tested for proviral genomic DNA were all negative, we note that not all SCC biopsies were tested for proviral genomic DNA. Both participants with SCC had metastatic SCC but neither had a biopsy of the metastatic SCC tested for proviral DNA. This was confirmed by the Sponsor in an IR response submitted to STN 125807/0.37 on March 11, 2024. Both participants had negative RCR tests throughout.*

5.2.3 Clinical study EB-101-LT-001

- i. Most common AEs: The most common TEAEs were wound infection (in non-study wounds (n=4), procedural pain (n= 2), squamous cell carcinoma (n=2), insomnia (n=2), and anemia (n=2).
- ii. SAEs: Six participants had 10 serious TEAEs, with three participants requiring new or prolonged hospitalization. No SAEs led to withdrawal from this study. One participant developed ascites on day 732 and 862 after Zevaskyn as well as vena cava thrombosis and ascites on day 971 after Zevaskyn treatment. These were felt to be unrelated to treatment by the investigator. There were no serious TEWAEs in this study. Squamous cell carcinoma events were considered serious and are described below in AESIs.
- iii. Deaths: To date, there have been no deaths after enrollment in this study.
- iv. AESIs:
 - a. SCC: Three patients had four SCC events but they were not at the treatment site and were considered not related to Zevaskyn treatment by the sponsor. Two of the patients with SCC had biopsy samples analyzed for proviral genome sequences which were negative. Both SCC events in the third patient are ongoing as of the data lock point but no biopsy or testing for genome sequences have been performed to date.

***Reviewer Comment:** Most of the TEAEs and TEWAEs are expected and/or related to underlying disease. As mentioned for the previous study, not all SCC biopsies have had testing for proviral genome sequences and therefore relationship to the treatment is difficult to assess.*

6 SPONSOR'S PHARMACOVIGILANCE PLAN

Table 2. Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Risk Identification and Mitigation Actions
Identified	Wound infection	<ul style="list-style-type: none"> Ongoing LTFU study EB-101-LT-001 up to 15 years post-treatment.

		<ul style="list-style-type: none"> • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Identified	Procedural pain	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities • Routine communication of safety information and risks
Identified	Pruritus	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Post-marketing safety study up to 15 years post-treatment • Routine pharmacovigilance activities • Routine communication of safety information and risks
Potential	Insertional oncogenesis	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Post-marketing safety study up to 15 years post-treatment with testing algorithm for viral genome • Expedited reporting for post-treatment malignancies • Summary/analysis of malignancies, based on interval and cumulative data, in periodic safety reports
Potential	Anemia exacerbation	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Potential	Postoperative hemorrhage	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Potential	Vomiting	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Potential	Immune reaction	<ul style="list-style-type: none"> • Potent topical steroids or other immune-modulating topical treatments for immunologic rejection. • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment.

		<ul style="list-style-type: none"> • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Potential	Risk associated with general anesthesia	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Potential	Risk associated with commercially available drugs used for biopsy	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment. • Routine pharmacovigilance activities. • Routine communication of safety information and risks
Missing	Safety in pregnant or breastfeeding persons	<ul style="list-style-type: none"> • Ongoing LTFU study EB-101-LT-001 up to 15 years post treatment.

*Adapted from Table 3, Pharmacovigilance Plan, STN 125807/0, Module 1.16.1, and Table 1, Response to Information Request submitted to STN 125807/0.13, Module 1.11.3 on Dec 13, 2023

Reviewer Comment: Due to the potential for gene therapies using integrating vectors to be associated with insertional oncogenesis, enhanced pharmacovigilance activities such as expedited reporting and analysis of post-treatment malignancies in periodic safety reports are warranted. Genetic analysis of post-treatment malignancies, particularly all squamous cell carcinomas, including those not in the treated areas is recommended. In an IR response submitted to STN 125807/0.30 on February 20, 2024, a revised pharmacovigilance plan was submitted (version 2.0) in which the potential risk 'Squamous Cell Carcinoma' was changed to 'Insertional Oncogenesis'. Details of testing for post-treatment malignancies are included in the next section.

6.1 Safety-related Post-marketing Study

In addition to the LTFU studies of participants in the clinical trials, in an IR submitted to STN 125807/0.13 on December 22, 2023, the Sponsor proposes a prospective, observational post-marketing registry study to specifically capture adverse event data from treated patients who receive commercial Zevaskyn product, post-licensure to provide up to 15 years of safety observation. The study will monitor for additional clinically important AEs not yet identified as a part of the Zevaskyn safety profile. Patients will be followed for 15 years post-treatment.

Study Objective: To evaluate the long-term safety of Zevaskyn (LZRSE-Col7A1 Engineered Autologous Epidermal Sheets [LEAES]) in individuals who received Zevaskyn treatment for RDEB in the post-marketing setting. In an IR response

submitted by the Sponsor to STN 125807/0.30 on February 20, 2024, the Sponsor specified the additional study objective:

To assess the occurrence of cutaneous malignancies after treatment with PZ in individuals who received PZ treatment for RDEB in the post-marketing setting.

Reviewer Comment: Should the product be approved, the study objective should include all malignancies after treatment with prademagene zamikeracel.

Study Participants: The study plans to enroll a minimum of 100 patients treated in the post-market setting. In an IR response submitted to STN 125807/0.34 on March 7, 2024, the Sponsor stated that there are approximately 3850 patients with RDEB in the United States and that they expected up to 250 patients to be treated and to be eligible to participate in the registry.

Inclusion criteria: -Consent by patient/guardian
 -Receipt of Zevaskyn treatment

Exclusion criteria: -Inability to properly follow registry protocol as determined by the Principal Investigator
 -Currently enrolled in an interventional clinical trial involving an investigational medicinal product to treat RDEB

Safety Endpoints:

- Primary safety endpoints:
 - Number and incidence of new cases of SCC after Zevaskyn treatment
 - Number and incidence of any new malignancies after Zevaskyn treatment.
- Secondary safety endpoints:
 - Number and incidence of treatment-emergent SAEs, including systemic and wound specific adverse events
 - Number and incidence of treatment-emergent SAEs related to Zevaskyn, including systemic and wound specific adverse events

In the IR response submitted to STN 125807/0.30 on February 20, 2024, patients with cutaneous malignancies at a treated site would have investigations done (biopsy for genomic testing and whole blood for RCR) if possible.

Reviewer Comment: Should the product be approved, the sponsor should attempt to obtain tissue for all post-treatment malignancies after prademagene zamikeracel. The sponsor should have clear procedures for sampling of tissue, assessment of vector persistence, and procedures for insertion site analysis.

Data Analysis: Data analysis will be descriptive in nature; there are no formal study hypotheses and no sample size calculations. For the outcome measures of AESI and SAE, data analysis will include incidence rates or proportions with 2-sided 95% confidence intervals. Kaplan-Meier methods will be used to summarize overall and event free survival (with events in both treated and untreated locations).

Reviewer Comment: The sponsor submitted a draft study protocol for the registry study. Prademagene zamikeracel utilizes an integrating retroviral vector and has potential for the serious risk of secondary malignancy due to replication-competent retrovirus or insertional mutagenesis. As required by regulations under Section 901 of the Food and Drug Administration Amendments Act (FDAAA) and as described in CBER SOPP 8415: Procedures for Developing Post-marketing Requirements and Commitments, a Sentinel sufficiency assessment was conducted to determine the sufficiency (i.e., capability) of the CBER Sentinel program to characterize the serious risk of secondary malignancy associated with prademagene zamikeracel. The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to characterize the serious risk of secondary malignancy since 15 years of follow-up, and collection of clinical samples and laboratory testing is needed; this is not feasible in available databases.

Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, the sponsor will be required to conduct a PMR safety study under FDAAA Title IX to identify the serious risk of secondary malignancy after treatment with prademagene zamikeracel. The PMR will be conducted for 15 years in accordance with the FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (January 2020).

OBPV/DPV presented the PMR to the CBER SWG on March 14, 2024 and received SWG concurrence for requiring a PMR safety study to assess the serious risk of secondary malignancy following administration of prademagene zamikeracel. The review team has since decided to issue a Complete Response (CR) letter due to multiple chemistry, manufacturing and control issues. The sponsor will be notified of the PMR in the CR letter.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Risk 1: Wound Infection

The risk of wound infection is innate to the disease process as well as a risk related to the product. The recommendation will be for any patient with a wound infection to be treated per standard of care using topical or systemic antibiotics as determined by bacterial culture and clinical judgment. In addition to routine pharmacovigilance activities and routine communication of safety information and risks, the Sponsor proposes to follow all patients in both the LTFU studies and the post-marketing registry.

7.1.2 Risk 2: Procedural Pain

Procedural pain is associated with both the surgical procedure and wound dressing changes. The recommendation is to manage pain per standard of care. Routine

pharmacovigilance activities and communication of safety information and risks will be performed.

7.1.3 Risk 3: Pruritus

Pruritus is commonly seen as the wounds heal and should be managed according to standard of care. Communication of this effect will be including in the prescribing information, instructions for use, and packaging and labels. Routine pharmacovigilance activities will be performed.

7.2 Important Potential Risks

7.2.1 Risk 1: Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma is a known feature of disease progression. Monitoring of all patients for any suspicious wounds will be recommended; if an SCC is identified, the recommendation will be made to remove it surgically and collect a sample for isolation of genomic DNA for detection of proviral genome sequences. This will enable determination if the SCC is related to Zevaskyn or to the underlying RDEB disease process. In addition to routine pharmacovigilance activities and these recommendations, this risk will be further assessed in the PMR described above.

Reviewer Comment: In an IR response submitted to STN 125807/0.30 on February 20, 2024, a revised pharmacovigilance plan was submitted (version 2.0) in which the potential risk 'Squamous Cell Carcinoma' was changed to 'Insertional Oncogenesis'.

7.2.2 Risk 2: Anemia exacerbation

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage anemia according to standard of care.

7.2.3 Risk 3: Postoperative hemorrhage

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage postoperative hemorrhage according to standard of care.

7.2.4 Risk 4: Vomiting

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage vomiting according to standard of care.

7.2.5 Risk 5: Immune reaction

Inflammatory wounds should be assessed using routine biopsy with hematoxylin and eosin and direct immunofluorescence to assess for immune rejection. In addition to routine pharmacovigilance activities, safety information and instructions for combinations of systemic and topical therapy will be communicated.

7.2.6 Risk 6: Risk associated with general anesthesia

Zevaskyn will only be administered in select qualified sites to ensure an experienced anesthesiologist will be available to administer general anesthesia.

7.2.7 Risk 7: Risk associated with commercially available drugs for biopsy

A recommendation will be communicated to avoid drugs known to cause irritation, sensitization, or severe skin irritations based on prior medical history.

7.3 Important Missing Information

7.3.1 Missing Information 1: Use in pregnant or breastfeeding women

Routine pharmacovigilance activities will be performed, including evaluation of pregnancy and/or breastfeeding cases. The lack of safety information in this population will be communicated in the prescribing information.

8 DPV ASSESSMENT

Based on review of the data submitted in this BLA, the primary concern to address in the post-marketing context is insertional oncogenesis. At the present time, the data from the clinical trials has not resulted in any documented cases of malignancy with the proviral genome present. However, given the class risk and the low number of patients in the clinical trials, this risk needs to be further examined should the product be approved.

9 DPV RECOMMENDATIONS

OBPV/DPV has reviewed the sponsor's proposed pharmacovigilance plan (version 2.0) for prademagene zamikeracel. At this time, the review team has decided to issue a CR letter outlining review issues. The review team and SWG have concurred on a FDAAA Title IX PMR study for which the sponsor is being notified in the CR letter:

- A postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies, and long-term safety, following treatment with prademagene zamikeracel. This study will enroll a minimum of 100 patients and each enrolled patient will be followed for 15 years after product administration.

OBPV/DPV final recommendations regarding the PVP and any possible additional safety-related postmarketing requirement or postmarketing commitment studies, REMS, or additional pharmacovigilance action(s) (such as enhanced pharmacovigilance with expedited reporting for events of special interest) will be deferred until further information is available and the response to the CR letter is received.

APPENDIX 1

Materials Reviewed

Table 1: Materials reviewed in support of this assessment

Date	Source	STN	Document(s) Reviewed
Sept. 25, 2023	Sponsor	125807/0	Module 1.16.1 Pharmacovigilance Plan
Sept. 25, 2023	Sponsor	125807/0	Module 1.14.1.3 Draft Labeling Text
Sept. 25, 2023	Sponsor	125807/0	Module 2.5 Clinical Overview
Sept. 25, 2023	Sponsor	125807/0	Module 2.7.4 Summary of Clinical Safety
Sept. 25, 2023	Sponsor	125807/0	Module 2.7.6 Synopses of Individual Studies
Sept. 25, 2023	Sponsor	125807/0	Module 5.3.5.1 Study Report of Study EB-101-CL-301
Sept. 25, 2023	Sponsor	125807/0	Module 5.3.5.1 Study Report of Study EB-101-LT-001
Sept. 25, 2023	Sponsor	125807/0	Module 5.3.5.2 Study Report of Study EB-101-Phase 1/2a
Sept. 25, 2023	Sponsor	125807/0	Module 5.3.5.3 Integrated Summary of Safety
Dec. 22, 2023	Sponsor	125807/0.13	Module 1.11.3 Response to Information Request
Feb. 20, 2024	Sponsor	125807/0.30	Module 1.11.3 Response to Information Request
Mar. 7, 2024	Sponsor	125807/0.34	Module 1.11.3 Response to Information Request
Mar. 11, 2024	Sponsor	125807/0.38	Module 1.11.3 Response to Information Request
Feb. 20, 2024	Sponsor	125807/0.30	Module 1.16.1 Pharmacovigilance Plan version 2.0