Statistical Analysis Plan

Sponsor Name:	Amryt Research Ltd.
Protocol Number and Title:	**BEB-13** **Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa**
Protocol Version and Date:	**Final Version 6.0, 18 April 2019** **(supersedes Version 5.0, 01 October 2018)**
Syneos Health Project Code:	**1008121**
Author:	[redacted], Senior Biostatistician [redacted] Senior Biostatistician
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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
1.0	30-MAR-2017	[redacted]	Initial Release Version
2.0	29-Nov-2018	[redacted]	Update after Protocol Version 5.0
3.0	27-Feb-2020	[redacted]	Update after Protocol Version 6.0 and CRF Version 5.0. VAS correction for the relevant Leuven itch subscores added. Analysis of Leuven Itching total score deleted. Pooled adverse event analysis after DB lock of OLP added. Subgroup analyses for Efficacy and Safety added. Additional efficacy analysis for open label phase added. Tables, listings and figures indexes deleted.
4.0	10-Jul-2020	[redacted]	Updates due to changes in the conduct of the study or planned analyses due to COVID 19 pandemic and further details added in some analyses methods of double blind phase endpoints.
5.0	01-Jul-2021	[redacted]	Updates due to requirements for additional interim analyses (FDA 90-Day Safety Update and EMA request to provide interim Open-label Phase efficacy analysis). List of outputs updated to reflect all outputs delivered, including post-hoc outputs. Other administrative changes.
6.0	09-Sep-2022	[redacted]	Visit windowing updated for the Month 12 and Month 24 visits as it was noted that the investigator sites generally use a year as 365 days, and not 360 days as utilised in the previous versions of the SAP.

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
[redacted] Senior Biostatistician	Sep 9, 2022 **Date (dd-Mmm-yyyy)**
[redacted] Principal Biostatistician	Sep 12, 2022 **Date (dd-Mmm-yyyy)**
Amryt Research Ltd.	
[redacted] Head of Clinical Development, Amryt Pharma	Sep 9, 2022 **Date (dd-Mmm-yyyy)**

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
BG	Blood glucose
BMI	Body Mass Index
BSAP	Body surface area percentage
Ca	Calcium
CAS	Completer Analysis Set
CCC	Confirmation of complete closure (of EB target wound)
CHW	Cui, Hung, Wang
CI	Confidence interval(s)
Cl	Chloride
cm	Centimetre
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
D	Day(s)
DBP	Double-blind Phase
DEB	Dystrophic epidermolysis bullosa
EB	Epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation	Description
EDBP	End of Double-blind Phase
eGFR	Estimate glomerular filtration rate
EOLP	End of Open-label Phase
EQ-5D	EuroQol 5 Dimensions
FAS	Full analysis set
FLACC	Face, Legs, Activity, Cry, Consolability
g	Gram(s)
GGT	Gamma-glutamyl transpeptidase
HRQoL	Health-related Quality of Life
IA	Interim Analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
iscorEB	Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa
JEB	Junctional epidermolysis bullosa
K	Potassium
kg	Kilogram(s)
LLT	Lowest Level Term
M	Month(s)
MAR	Missing at Random
max	Maximum
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
min	Minimum
mm	Millimetre
MNAR	Missing not at Random
n	Number of observations
Na	Sodium
OLP	Open-label Phase
OR	Odds ratio
P	Phosphate

Abbreviation	Description
PK	Pharmacokinetics
PPS	Per-protocol set
PRO	Patient-reported outcome
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TBSA	Total body surface area
TEAE	Treatment Emergent Adverse Events
TSQM	Treatment Satisfaction Questionnaire for Medication
TLF	Table, Listing and Figure
VAS	Visual Assessment Scale
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which are produced, and the statistical methodologies that are used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Syneos Health perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings (TLFs).

2.2. TIMINGS OF ANALYSES

This study includes interim safety reviews (blinded and unblinded), an interim analysis (IA) with sample size re-estimation for the Independent Data Monitoring Committee (IDMC), additional interim OLP analyses (unblinded after completion of DBP), a final primary analysis of the double-blind treatment period and a follow-up analysis of the open-label treatment period.

The IDMC was established to review and evaluate primary efficacy and safety data during the double-blind phase (DBP) of the study. The committee consists of independent experts who are not involved in the study. Interim IDMC safety reviews are conducted to ensure safety for participants and to advise regarding continuation, modification, or discontinuation of individual patients and/or of the futility of the study. Blinded safety reviews could occur any time should questions of patient safety arise during the DBP and to review Serious Adverse Events (SAEs) that require expedited reporting to a regulatory agency. An IDMC unblinded interim safety review (26 February 2019) which included review of pharmacokinetic (PK) data was planned when at least 6 children between 4 and 11 years would have had completed 90 days of DBP, plus at least the same number of older children and adults. A total of 38 patients were included in this analysis, with 15 patients between 4 and 11 years, 7 patients for 12 and 17 years, and 16 adults. Following this review, the IDMC recommended to expand the inclusion of children with Epidermolysis Bullosa (EB) to all ages i.e. ≥21 days and <4 years. The unblinded IA for sample size re-estimation took place when approximately 50% of patients completed D45±7 (21 December 2018). Based on the results of the sample size re-estimation, the IDMC recommended to increase the sample size by 48 patients (24 per arm) to a total of 230 evaluable patients (i.e., patients eligible to be included in the primary efficacy analysis; see Section 9.2 for more details). In total, 250 patients were planned to be enrolled and treated in the study to account for patients who drop-out.

On 6th March 2020, 223 patients had been enrolled into the study and in the preceding months the rate of enrolment had slowed, which reflects the low number of patients with this rare disease. From February 2020, the COVID-19 pandemic impact escalated with hospitals across the globe focusing on these infected patients and non-emergency visits were severely restricted or cancelled. Hence, new patients' enrolment would be further reduced or cease for an unclear and probably long period of time. The Sponsor took advice

from an independent expert and concluded that the statistical impact of further patient recruitment would most likely be negligible. In addition, by stopping accrual of new patients and avoiding a potentially long hiatus in study accrual, the evaluation of Oleogel-S10 treatment for patients with a very high unmet medical need could be undertaken. The Sponsor decided to cease enrolment with the last patients first visit on 6th March 2020 and would then proceed to database lock of the double-blind phase.

The first full statistical analyses of the study was performed after all data up to the end of double-blind phase (EDBP) visit (D90±7) have been entered and cleaned, a database lock of these data has been performed and unblinding has been done. In addition, interim open-label phase (OLP) safety data (adverse events including subgroup analyses, local tolerability and laboratory data) available at EDBP will be analysed. The final IDMC meeting was held after this on 10-Nov-2020.

An additional safety OLP interim analysis was performed when all ongoing patients had completed their Month 9 visits. After the ongoing patients had all their data up to the Month 9 visit (M9±14) entered and cleaned, a database lock of this data was performed. This is an unblinded analyses, as the study was unblinded after the first full statistical analysis.

An additional efficacy and safety OLP interim analyses will be performed when all ongoing patients have had their Month 12 visits. This is the second full statistical analysis to be performed for the study. After the ongoing patients have all their data up to the Month 12 visit (M12±14) entered and cleaned, a database lock of this data will be performed. This is an unblinded analyses, as the study was unblinded after the first full statistical analysis.

The statistical analyses of efficacy and safety for the complete OLP together with analyses of efficacy and safety for the full study are performed after database lock of the OLP.

2.3. REPORTING AND TERMINOLOGY

The Clinical Study Report (CSR) for this study will be prepared in 2 parts; the CSR (DBP) which is prepared at the EDBP and reports efficacy and safety of the DBP and interim OLP safety data (adverse events including subgroup analyses, local tolerability and laboratory data) available at DBP database lock; and the CSR (OLP) which is prepared at the end of the Open-Label Phase (EOLP) and reports efficacy and safety for the OLP.

During the DBP of the study, visits are named numerically (Visits 1-7a) and descriptively based on the scheduled study day (D) (D0, D7, etc. up to D90). Visit 7a/D90±7d is the EDBP and this corresponds to the first visit of the OLP phase (Visit 7b)/OLP D0. Numerical visit numbering continues throughout the OLP (Visits 7b-10); visit naming during the OLP is in month (M) intervals relative to the start of the OLP, hence OLP Visit 8, M3±14d is 90 days from the start of the OLP or 180 days from the start of the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the DBP is to compare the efficacy of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B) in the promotion of healing of Epidermolysis Bullosa (EB) partial thickness wounds. This is assessed as evidenced by the incidence of the first complete closure of the EB target wound (defined as EB partial thickness wound of 10 cm^2 to 50 cm^2 in size aged ≥21 days and <9 months) in patients with inherited EB (subtypes Junctional epidermolysis bullosa [JEB], Dystrophic epidermolysis bullosa [DEB], or Kindler syndrome) within 45±7 days of treatment.

3.2. SECONDARY OBJECTIVES

The secondary objectives of the DBP are to:

- Compare the efficacy of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B) as evidenced by:
  - The time to first complete closure of the EB target wound in either arm within 90±7 days of treatment
  - The incidence of first complete closure of the EB target wound over time
  - The relative change from baseline in EB target wound size over time
  - The relative change from baseline in total body wound burden over time
  - The relative change from baseline in percentages of total body surface area (TBSA) affected by EB partial thickness wounds over time
  - The incidence and severity of wound infection over time
  - The change from baseline in “background” pain before wound dressing changes and the change from baseline in “procedural” pain after wound dressing changes over time
  - The change from baseline in itch before wound dressing changes over time
  - The change from baseline in impact of wounds on sleep over time (in patients ≥14 years of age)
  - The number of days missed from school or from work
  - The response to treatment as assessed by patients ≥14 years of age using the Treatment Satisfaction Questionnaire for Medication (TSQM).
- Compare the safety of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B) as evidenced by the incidence, severity, and relatedness of Adverse Events (AEs), and based on laboratory assessments.
- Compare the tolerability of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B).

- Assess betulin exposure

The objectives of the 24-month OLP are listed below as stated in the protocol, however, some have changed as discussed in Section 12. The main change is the removal of the assessment of change from DBP baseline for the OLP safety and efficacy parameters since data from the DBP and OLP will be analysed separately.

- Evaluate the safety of Oleogel-S10 as evidenced by the incidence, severity, and relatedness of AEs and based on laboratory assessments
- Evaluate local tolerability of Oleogel-S10
- Assess betulin exposure
- Assess the proportion of patients with complete closure of the EB target wound at M3±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in total body wound burden at M3±14 days, M12±14 days, and M24±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in percentages of TBSA affected by EB partial thickness wounds at M3±14 days, M12±14 days, and M24±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in "background" pain before wound dressing changes and the change from baseline in "procedural" pain after wound dressing changes at M3±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in itch before wound dressing changes at M3±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in impact of wounds on sleep (in patients ≥14 years of age) at M3±14 days
- Assess the number of days missed from school or from work at M3±14 days
- Assess the changes from baseline of both DBP (D0) and OLP (D0)/EDBP (D90±7) in treatment satisfaction (in patients ≥14 years of age) at M3±14 days
- Assess the changes from EDBP (D90±7) in disease severity from both the clinician and patient/family perspective at M12±14 days and M24±14 days
- Assess the changes from EDBP (D90±7) in patients' quality of life at M12±14 days and M24±14 days

3.3. BRIEF DESCRIPTION

This is a 2-part phase III study with a double-blind, randomised, vehicle-controlled phase to compare the efficacy, safety and tolerability of Oleogel-S10 (treatment arm A) versus vehicle (treatment arm B) in patients with inherited EB (subtypes JEB, DEB, or Kindler syndrome). Eligible patients who meet all inclusion criteria and none of the exclusion criteria (Protocol Section 5) enter the double-blind phase (DBP) at Day 0 (DBP D0). The Investigator selects the target wound and up to 4 additional wounds that meet target

wound criteria (non-target wounds). At the End of DBP (EDBP) Visit on D90±7, patients in both treatment arms enter the single-arm, follow-up, open-label phase (OLP) with Oleogel-S10 until the End of OLP (EOLP) Visit on M24±14d. The EDBP Visit will thus coincide with the OLP Day 0.

Each patient participates for 90±7 days in the randomised DBP. Each patient in the OLP receives Oleogel-S10 treatment for 24 months. The total study duration (DBP and OLP) is approximately 27 months.

Safety and local tolerability are monitored and documented continuously throughout the study. The End of Study is defined as completion of the last visit or assessment for the last patient.

The study procedures and the examinations performed at each visit are displayed in the Flowchart in Table 1. For additional information on study design refer to Protocol section 4.2.

Table 1. Flowchart of Study (Randomised, Double-blind and Follow-up, Open-label Phase)

Examination	Screening	Randomised, Double-blind Phase (DBP)						Follow-up, Open-label Phase (OLP)			
			3 months					24 months			
			Intervention Period					Intervention Period			
		Baseline	Site Visit or Home Visit (Study Team Member)	Site Visit				Site Visit		Interim Phone Calls[A]	Site Visit
Day (D)/Month (M)	**≤ D0 (up to 28 days)**	**DBP D0**	**D7 ±2d[B]**	**CCC[C]**	**D14±5d[D]/ D45±7d[D]**	**D30/ D60 (±7d)**	**EDBP (D90±7d) / OLP D0[E]**	**M3 ±14d**	**M12 ±14d**	**M6, M9, M15, M18, M21 (±28d)**	**EOLP (M24±14d)**
Visit	–	1	2	+	3/5	4/6	7a/7b	8	9	–	10
Eligibility assessments											
▪ Informed consent[F]	X	(X)[G]									
▪ Inclusion/exclusion criteria		X									
▪ Demographics, medical history incl. EB subtype and optional genetic analysis[H]		X									
▪ Physical examination, selection of EB target wound at D0		X					X				X
Stratified randomisation		X									
Patient-reported outcomes											
▪ Itch Man Scale (≥ 4 to 13 y) or Leuven Itch Scale (≥ 14 y)		X	X[I]			X	X	X			
▪ FLACC scale (<4 y) or Wong Baker FACES Scale (≥ 4 y)[J]		X	X[I]		X	X	X	X			
▪ W-QoL – impact of wounds on sleep (≥ 14 y)		X	X[I]			X	X	X			

Examination	Screening	Randomised, Double-blind Phase (DBP)						Follow-up, Open-label Phase (OLP)			
			3 months					24 months			
		Baseline	Intervention Period					Intervention Period			
			Site Visit or Home Visit (Study Team Member)	Site Visit				Site Visit		Interim Phone Calls[A]	Site Visit
Day (D)/Month (M)	**≤ D0 (up to 28 days)**	**DBP D0**	**D7 ±2d[B]**	**CCC[C]**	**D14±5d[D]/ D45±7d[D]**	**D30/ D60 (±7d)**	**EDBP (D90±7d) / OLP D0[E]**	**M3 ±14d**	**M12 ±14d**	**M6, M9, M15, M18, M21 (±28d)**	**EOLP (M24±14d)**
Visit	**–**	**1**	**2**	**+**	**3/5**	**4/6**	**7a/7b**	**8**	**9**	**–**	**10**
▪ Question on number of days missed from school or work		X			X	X	X	X			
▪ Treatment Satisfaction Questionnaire (≥ 14 y)			X[I]			X	X	X			
▪ iscorEB[K]							X		X		X
▪ EQ-5D							X		X		X
Efficacy assessments											
▪ Estimation of total body wound burden (EBDASI, Section I)		X				X	X	X	X		X
▪ BSAP affected by EB partial thickness wounds		X				X	X	X	X		X
▪ Target wound photography (ARANZ Silhouette® system)		X	X[I]	X	X	X	X	X			
▪ Photography of other wounds matching target wound criteria		X	X[I]		X	X	X	X			
▪ Closure of target wound (clinical assessment) [L]				X[M]	X	X	X	X			
▪ Closure of target wound (patient assessment)			X		X	X	X				

Examination	Screening	Randomised, Double-blind Phase (DBP)						Follow-up, Open-label Phase (OLP)			
			3 months					24 months			
		Baseline	Intervention Period					Intervention Period			
			Site Visit or Home Visit (Study Team Member)	Site Visit				Site Visit		Interim Phone Calls[A]	Site Visit
Day (D)/Month (M)	**≤ D0 (up to 28 days)**	**DBP D0**	**D7 ±2d[B]**	**CCC[C]**	**D14±5d[D]/ D45±7d[D]**	**D30/ D60 (±7d)**	**EDBP (D90±7d) / OLP D0[E]**	**M3 ±14d**	**M12 ±14d**	**M6, M9, M15, M18, M21 (±28d)**	**EOLP (M24±14d)**
Visit	–	1	2	+	3/5	4/6	7a/7b	8	9	–	10
Safety laboratory tests											
▪ Full blood count with white blood cell differential	X	(X)[N]					X		X		X
▪ Serum electrolytes (Na, K, Ca, Cl, P), glucose, urea, creatinine, betulin levels[O]	X	(X)[N]					X		X[P]		X
▪ Serum total protein, albumin, ALT, AST, AP, GGT	X	(X)[N]					X		X		X
▪ Urine pregnancy test[Q]	X	X[R]					X	X	X		X
▪ Voluntary blood test for betulin analysis		X[S]	X[I]	X	X	X	X[S]	X			X[S]
Study medication dispensing/redispensing		X			X	X	X	X	X	(X)[A]	
Study medication + non-adhesive wound dressing[T]		X	X[I]	X[U]	X	X	X	X	X		
Return of study medication					X	X	X	X	X	(X)[A]	X
Frequency of dressing change, application method, type of dressing		X	X		X	X	X	X	X	X	X
Safety assessments											
▪ Vital signs (heart rate, respiratory rate, body temperature)		X					X				X
▪ Electrocardiogram		X					X				X
▪ Concomitant medication		Continuously throughout the study									

Examination	Screening	Randomised, Double-blind Phase (DBP)						Follow-up, Open-label Phase (OLP)			
			3 months					24 months			
			Intervention Period					Intervention Period			
		Baseline	Site Visit or Home Visit (Study Team Member)		Site Visit			Site Visit		Interim Phone Calls[A]	Site Visit
Day (D)/Month (M)	≤ D0 (up to 28 days)	DBP D0	D7 ±2d[B]	CCC[C]	D14±5d[D]/ D45±7d[D]	D30/ D60 (±7d)	EDBP (D90±7d) / OLP D0[E]	M3 ±14d	M12 ±14d	M6, M9, M15, M18, M21 (±28d)	EOLP (M24±14d)
Visit	–	1	2	+	3/5	4/6	7a/7b	8	9	–	10
▪ AE/SAE assessment, local tolerability		Continuously throughout the study									
Withdrawal from study		D90±7d or M24±14d Visit Assessments should be conducted for DBP or OLP phase, respectively									

AE = Adverse event; ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase; BSAP = Body surface area percentage; Ca = Calcium; CCC = Confirmation of complete closure (of EB target wound); Cl = Chloride; D = Day; d = days; EB = Epidermolysis bullosa; EBDASI = EB Disease Activity and Scarring Index; EDBP = End of Double-blind Phase; EOLP = End of Open-label Phase; EQ-5D = EuroQol 5 Dimensions; FLACC = Face, Legs, Activity, Cry, Consolability; GGT = Gamma-glutamyl transpeptidase; K = Potassium; Na = Sodium; P = Phosphate; SAE = Serious adverse event; W-QoL = Wound Quality of Life Questionnaire; y = Year(s)

A. A site visit can be scheduled instead of an interim phone call to facilitate dispensing and return of study medication.

B. D7±2 visit can also be a phone call instead of a site or home visit.

C. CCC visit: **C**onfirmation of **C**omplete **C**losure of the EB target wound 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound in the Double-blind phase...

D. Alternatively, the investigator may visit the patient at home on D14±5d, and D45±7d.

E. The first day of the follow-up open-label phase (OLP D0) occurs at visit EDBP (D90±7d).

F. An optional informed consent form for collection blood samples for betulin analysis and an optional consent form for genetic testing to determine EB subtype are provided to the patient at screening. If the patient consents to the optional collection of blood samples for betulin analysis, written consent should be obtained at the baseline visit, if not already provided at the screening visit. Written informed consent for optional genetic testing can be obtained at any visit during the study.

G. If not obtained at screening.

H. Optional genetic testing procedures can be carried out at any visit, if the patient has provided consent.

I. Assessment is performed if patient has site visit or home visit at D7±2. If the patient has phone call, the assessment is not performed.

J. “Background” pain is measured before dressing change; “procedural” pain is measured after dressing change using either the FLACC scale or the Wong-Baker FACES.

K. iscorEB should only be completed if available in the local language.

L. Assessment of wound status and wound size should be in comparison to baseline (DBP) and not the previous visit. Worsening of wound status, increase in wound size, re-opening of wounds and wound infections should be reported as AEs.

M. Investigator to confirm closure of target wound from assessment of target wound photography.

N. If haematology and biochemistry parameters have been determined within 4 weeks prior to baseline, they may be used as baseline values. (Note: The blood draw must occur prior to study medication exposure.)

O. Betulin analyses from safety laboratory blood samples do not require additional consent.

P. Betulin levels are not required at M12 visit.

Q. In women of childbearing potential/postmenarchal female adolescent patients only.

R. If a pregnancy test has been performed within 14 days prior to baseline it does not need to be repeated at baseline.

S. No additional voluntary sample is required if blood sample for safety laboratory test is to be taken at the same visit. Blood samples for safety laboratory tests can be used for betulin analysis.

T. Study medication and wound dressing changes performed at home except for site visits.

U. If the EB target wound (or other wound matching target wound criteria) is confirmed as closed, it is not necessary to continue to apply study medication. The area may be dressed to protect the skin. Study medication continues to be applied to any other EB partial thickness wounds.

3.4. DETERMINATION OF SAMPLE SIZE

The assumed true control rate for the primary endpoint of first complete closure of the EB target wound is 27%. Based on the use of a two-sided chi-square test of equality of binomial proportions at the alpha=0.05 level of significance, a total sample size of 182 patients (91 patients per arm) provides 80% power to detect an improvement of 20 percentage points (i.e., a true Oleogel-S10 rate of 47%). A total of 192 patients was planned to be enrolled into the study and treated to account for a drop-out rate of 5%, as drop-out rates in studies with EB patients are reported to be small (Paller, Browning et al. 2016).

The Cochran-Mantel-Haenszel (CMH) test was not used for the sample size estimation since there is no valid information available about expected response rates within the strata.

Following the unblinded interim analysis on 21 December 2018, the IDMC recommended that the sample size should be increased by 48 patients (24 per arm) to a total of 230 evaluable patients. It is planned to enrol and treat a total of 250 patients to account for drop-outs.

3.5. TREATMENT ASSIGNMENT & BLINDING

Patients are stratified according to their EB subtype and size of target wound (cm^2) to the following groups: JEB/Kindler 10 to <20; JEB/Kindler 20 to <30; JEB/Kindler 30 to 50; DEB 10 to <20; DEB 20 to <30; or DEB 30 to 50 cm^2. Patients are then randomised 1:1 to receive either Oleogel-S10 (treatment arm A) or vehicle gel (treatment arm B). Investigators and patients both are blinded for treatment allocation. An independent unblinded biostatistics team maintains the randomisation scheme key and only distributes this to approved personnel. For the purpose of the IA for sample size re-estimation, the unblinded results were provided to the approved IDMC members by the independent unblinded biostatistics team.

During the OLP, all patients are treated with Oleogel-S10. Both the investigator and the patient know the treatment.

3.6. ADMINISTRATION OF STUDY MEDICATION

Study medication is administered to the EB target wound and to all areas on the patient's body that are affected by EB partial thickness wounds, then Standard of Care non-adhesive wound dressings are applied as described in Protocol sections 6.3 and 7, respectively.

4. ENDPOINTS OF DOUBLE-BLIND PHASE

The statistical analysis (efficacy and safety) of the DBP is performed after database lock of the DBP and is reported in the CSR (DBP).

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint of the DBP is:

1. Proportion of patients with first complete closure of the EB target wound (defined as EB partial thickness wound of 10 cm^2 to 50 cm^2 in size aged ≥21 days and <9 months) in patients with inherited EB (including subtypes JEB, DEB, or Kindler syndrome) within 45±7 days of treatment with Oleogel-S10 compared to vehicle based on clinical assessment by the investigator (the wound is rated as "closed" at first appearance of complete reepithelialisation without drainage)

4.2. SECONDARY EFFICACY ENDPOINTS

The key secondary (confirmatory) efficacy endpoints are:

1. Time to first complete closure of the EB target wound as evidenced by clinical assessment until EDBP (D90±7)
2. Proportion of patients with first complete closure of the EB target wound at D90±7 based on clinical assessment by the investigator
3. The incidence of wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection)
4. The maximum severity of wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection)
5. Change from baseline (DBP D0) in total body wound burden as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the 'EB Disease Activity and Scarring Index' (EBDASI) (Loh, Kim et al. 2014) at D90±7
6. Change from baseline (DBP D0) in itching using the 'Itch Man Scale' (Morris, Murphy et al. 2012) in patients ≥ 4 years and up to 13 years of age and the 'Leuven Itch Scale' in patients ≥ 14 years of age, before wound dressing changes at D90±7

Other secondary efficacy endpoints of the DBP are:

7. Proportion of patients with first complete closure of the EB target wound at D14±5, D30±7 and D60±7 based on clinical assessment by the investigator
8. Proportion of patients with first complete closure of the EB target wound at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7 based on patient assessment
9. Proportion of patients with first complete closure of the EB target wound at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7 based on blinded evaluation of photographs

10. Percentage change from baseline (DBP D0) in EB target wound size as evidenced by blinded evaluation of photographs taken at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7
11. Change from baseline (DBP D0) in total body wound burden as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the EBDASI (Loh, Kim et al. 2014) at D30±7 and D60±7
12. Change from baseline (DBP D0) in body surface area percentage (BSAP) of TBSA affected by EB partial thickness wounds as evidenced by clinical assessment based on the '*Lund and Browder*' chart (Miminas 2007) at D30±7, D60±7, and D90±7
13. Change from baseline (DBP D0) in "background" pain using the '*Face, Legs, Activity, Cry, Consolability*' (FLACC) scale (Merkel, Voepel-Lewis et al. 1997) in patients <4 years of age and the '*Wong-Baker FACES® Pain Rating Scale*' (Wong-Baker 2015) in patients ≥4 years of age before wound dressing changes at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7
14. Change from baseline (DBP D0) in "procedural" pain using the FLACC scale (Merkel, Voepel-Lewis et al. 1997) in patients <4 years of age and the '*Wong-Baker FACES® Pain Rating Scale*' (Wong-Baker 2015) in patients ≥4 years of age after wound dressing changes at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7
15. Change from baseline (DBP D0) in itching using the '*Itch Man Scale*' (Morris, Murphy et al.2012) in patients ≥4 years and up to 13 years of age and the '*Leuven Itch Scale*' in patients ≥14 years of age before wound dressing changes at D7±2, D30±7 and D60±7
16. Change from baseline (DBP D0) in impact of wounds on sleep (in patients ≥14 years of age) as measured by differences in 11-point Likert scales at D7±2, D30±7, D60±7, and D90±7 (Blome, Baade et al. 2014)
17. The number of days missed from school or from work due to EB as reported by patients at D0 for the last 14 days and cumulatively for all visits until D90±7
18. Evaluation of the treatment response (in patients ≥14 years of age) using the TSQM, Version 9, before wound dressing changes at D7±2, D30±7, D60±7, and D90±7 (Bharmal, Payne et al. 2009)

4.3. SAFETY ENDPOINTS

The safety endpoints of the DBP are:

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Vital signs
- Electrocardiograms (ECGs)
- Systemic betulin exposure data

5. ENDPOINTS OF OPEN-LABEL PHASE

The statistical analysis (efficacy and safety) of the completed OLP is performed after database lock of the OLP and is reported in the CSR (OLP). Interim OLP safety data (adverse events including subgroup analyses, local tolerability and laboratory data) available at DBP database lock will be reported in the CSR (DBP).

5.1. EFFICACY ENDPOINTS

- The maximum severity of wound infection between OLP baseline (OLP D0) and M24±14 days as evidenced by AEs and/or use of topical and/or systemic antibiotics that are related to wound infection
- Changes from OLP baseline (OLP D0) in total body wound burden as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the EBDASI (Loh, Kim et al. 2014) at M3±14 days
- Changes from OLP baseline (OLP D0) in BSAP of TBSA affected by EB partial thickness wounds as evidenced by clinical assessment based on the 'Lund and Browder' chart (Miminas 2007) at M3±14 days
- Changes from OLP baseline (OLP D0) in "background" pain using the FLACC scale (Merkel, Voepel-Lewis et al. 1997) in patients <4 years of age and the 'Wong Baker FACES® Pain Rating Scale' (Wong-Baker 2015) in patients ≥4 years of age before wound dressing changes at M3±14 days
- Changes from OLP baseline (OLP D0) in "procedural" pain using the FLACC scale (Merkel, Voepel-Lewis et al. 1997) in patients <4 years of age and the 'Wong-Baker FACES® Pain Rating Scale' (Wong-Baker 2015) in patients ≥4 years of age after wound dressing changes at M3±14 days
- Changes from OLP baseline (OLP D0) in itching using the 'Itch Man Scale' (Morris, Murphy et al. 2012) in patients ≥4 years and up to 13 years of age and the 'Leuven Itch Scale' in patients ≥14 years of age before wound dressing changes at M3±14 days
- Changes from OLP baseline (OLP D0) in impact of wounds on sleep (in the prior 7 days, in patients ≥14 years of age) as measured by differences in 11-point Likert scales at M3±14 days (Blome, Baade et al. 2014)
- The number of days missed from school or from work due to EB as reported by patients at M3±14 days for the last 14 days
- Evaluation of the treatment satisfaction (in patients ≥14 years of age) using the TSQM, Version 9, before wound dressing changes at M3±14 days (Bharmal, Payne et al. 2009)
- Changes from OLP baseline (OLP D0) in disease severity from both clinician and patient/family perspective as quantified with the Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa 'iscorEB' at M12±14 days and M24±14 days

- Changes from OLP baseline (OLP D0) in patients' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with the EuroQol 'EQ 5D' instrument at M12±14 days and M24±14 days
- Proportion of patients with complete closure of the EB target wound at M3±14 based on clinical assessment by the investigator and blinded evaluation of photographs, and at M12±14 days and M24±14 days based on clinical assessment only.

5.2. SAFETY ENDPOINTS

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Vital signs
- Electrocardiograms (ECGs)
- Systematic betulin exposure data

6. ANALYSIS SETS

The statistical analysis is based on the study populations described below.

Patients who are randomised but not treated are not assigned to any of the analysis sets.

6.1. SAFETY ANALYSIS SET

The Safety Analysis Set (SAF) includes all patients treated at least once with study medication. Patients are analysed according to the treatment regimen received (if different from the randomised treatment). The SAF is used for all analyses of safety endpoints and the presentation of the study population summaries and patient-level data listings.

6.2. FULL ANALYSIS SET

The Full Analysis Set (FAS) includes all randomised patients treated at least once with study treatment. Patients are analysed according to the randomised treatment regimen (if different from the received treatment). The FAS is used as the primary analysis set for all efficacy analyses.

6.3. COMPLETER ANALYSIS SET

The Completer Analysis Set (CAS) includes all patients from the FAS who did not discontinue the double-blind phase of the study early, irrespective of the reason for discontinuation. Patients are analysed according to the randomised treatment regimen.

Supportive analyses of the primary efficacy endpoint and key secondary endpoints are conducted using the CAS.

6.4. PER PROTOCOL SET

The Per Protocol Set (PPS) includes all patients who have met the eligibility criteria, received the planned study medication, and have reasonably adhered to all relevant protocol conditions. Patients are analysed according to randomised treatment regimen.

Case-by-case decisions regarding exclusions of patients from the PPS analysis are made prior to final unblinding in a Blind Data Review Meeting (BDRM) which is performed prior to database lock and unblinding of the DBP of the study.

Supportive analyses of the primary efficacy endpoint and key secondary endpoints are conducted using the PPS.

6.5. PROTOCOL DEVIATIONS

Protocol Deviation data are recorded on the electronic case report form (eCRF) by the sites. Protocol deviations are documented by type and categorised individually as major or minor. During the BRDM, these deviations are evaluated as important or non-important

to determine which patients are excluded from the PPS. Major and minor protocol deviations are listed and summarised. For minor protocol deviations the following deviation types will be included in the listing:

1. Visit: missed visit (CCC + 2 days, after Day 45±7 days), Outside Window (CCC + 2 days, after Day 45±7 days)
2. Study procedures: missed procedures, procedures outside window
3. Incorrect procedure/order

Patients that are incorrectly randomised to a stratum (i.e. EB subtype and wound size) are recorded as Protocol Deviations but are included in the correct stratum for all analyses. The correct strata are taken from the clinical database.

All protocol deviations regarding visits and assessments that have been modified due to the COVID-19 pandemic will be presented in a separate listing.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1. GENERAL METHODS

This study consists of interim safety reviews, an interim analysis (IA) with sample size re-estimation, a final primary analysis of the double-blind treatment period and a follow-up analysis of the open-label treatment period. See Section 2.2 for more details on the interim safety reviews and the IA with sample size re-estimation made by the IDMC.

The first full statistical analysis of the study is performed after all data up to the EDBP visit (D90±7) has been entered and cleaned, a database lock of these data has been performed and unblinding has been done. In addition, interim OLP safety data (adverse events including subgroup analyses, local tolerability and laboratory data) available at EDBP will be analysed and presented in the Clinical Study Report (DBP). The statistical analyses of efficacy and safety for the OLP are performed after database lock of the OLP and are reported in the Clinical Study Report (OLP).

An additional safety OLP interim analysis was performed when all ongoing patients had completed their Month 9 visits. After the ongoing patients had all their data up to the Month 9 visit (M9±14) entered and cleaned, a database lock of this data was performed. This is an unblinded analyses, as the study was unblinded after the first full statistical analysis.

An additional efficacy and safety OLP interim analyses will be performed when all ongoing patients have had their Month 12 visits. This is the second full statistical analysis to be performed for the study. After the ongoing patients have all their data up to the Month 12 visit (M12±14) entered and cleaned, a database lock of this data will be performed. This is an unblinded analyses, as the study was unblinded after the first full statistical analysis.

Data are presented in patient data listings using the SAF, except where noted. Data listings are ordered by treatment and patient identification number. Summary tables are presented by treatment and overall unless specified otherwise, and by study visit where applicable. For tables that are presented separately by study phase (e.g., medication and AEs), the treatment groups presented in the OLP are the randomised treatment groups during the DBP.

All categorical (binary and ordinal) data are summarised using frequency counts and percentages of patients. Percentages are calculated using the study population excluding patients with missing values as the denominator. Continuous variables are summarised using number of observations (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. All estimations include a point estimate and the corresponding two-sided 95% confidence interval (CI).

7.2. KEY DEFINITIONS

7.2.1. First Study Treatment Date

- For the DBP, the first randomised study treatment is administered at Baseline on Day 0 (DBP D0) which corresponds to the randomization date.
- For the OLP, the first study treatment is administered at Study Visit 7b (D90±7, OLP D0). Respective date is derived based on the information reported on the Open label drug dispensing eCRF page.

7.2.2. Last Study Treatment Date

- For the DBP, last study treatment date is the date the study medication was last used as reported in the DBP Completion eCRF page in the database.
- For the OLP, last study treatment date is the date the study medication was last used as reported in the OLP Completion eCRF page in the database.

For patients who are lost to follow-up, the last study treatment date is the date of the last visit when they attended.

7.2.3. Baseline, Change from Baseline and Relative Change from Baseline

For each study phase, baseline is the last value prior to or on the date of first study medication of that phase.

Changes from baseline and relative changes from baseline of the DBP and OLP are obtained, where applicable, as follows:

- Change from baseline = (post-baseline value – baseline value).
- Relative change from baseline (%) = (post-baseline value – baseline value) / (baseline value) * 100.

For the purpose of tabulations, the unscheduled post-baseline values are excluded.

For the DBP, changes from DBP baseline are calculated. For the OLP, changes from OLP baseline are calculated.

7.2.4. Study Day

The Study Day for both the DBP and OLP (chronologic) will be calculated based on the actual assessment date. For efficacy and safety data, study day (used for analysis visit windowing in Section 7.4) will be calculated relative to the date of first administration of study treatment in the DBP which corresponds to the randomisation date as follows:

- If the assessment date/event start date is prior to first treatment: Date of assessment – Date of first treatment

- If the assessment date/event start date is on/after first treatment: Date of assessment – Date of first treatment +1

Study day will be negative for assessment dates prior to first DBP treatment.

7.3. MISSING DATA

Care is taken during the conduct of this study to minimise the amount of missing data.

Note that changes in the assessment schedule have been made as a result of protocol amendments. Thus, some missing data are expected by design.

With respect to the endpoint of proportion of first wound closure at a specific visit x (including the primary endpoint), early withdrawals and patients discontinued due to target wound infection that are not available at visit x are considered as failures (wound not closed) if the EB target wound was not assessed as closed at a prior visit. If the wound was closed at a prior visit, the patient is considered a responder for visit x, although he/she was withdrawn or discontinued before visit x.

Withdrawn patients are not replaced and are evaluated according to their last visit. If no assessment is available after start of therapy, a missing data value is not replaced.

Complete missing or partial dates are presented in the listings as reported on eCRFs.

If an AE has a completely missing onset date, then the AE is considered as a Treatment Emergent Adverse Event (TEAE; starting in Treatment Period DBP at D0 visit). A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication.

If an adverse event or a medication has a partial missing start or stop date, the following rules are used to impute the date; then the imputed date is used to determine whether it is a TEAE for adverse event, or a prior or concomitant medication.

Table 2: Partial Date Derivation

Partial Missing Start or Stop Date	Derived Start Date	Derived Stop Date
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month derived as January or same as first dose month if the year is the same as the year of first dose	Missing month derived as December

Due to the COVID-19 pandemic, sites could deviate from the protocol schedule of assessments (e.g. missed study visits or scheduled assessments). In accordance with the guidelines released by regulatory health authorities, an Administrative Letter which serves as an addendum to protocol version 6 was prepared outlining that on-site patient visits could be performed as home visits or phone/ video calls in order to enable patients to continue in the study as intended. Instructions regarding how a patient's visits and assessments should be handled were sent to the sites. Nonetheless, missing data is still expected as a result of COVID-19. Any notable deviation from protocol v6 due to COVID-19 will be captured and evaluated in the CSR.

7.4. VISIT WINDOWS FOR EFFICACY ANALYSIS

All efficacy data will be identified by Study Day as defined in Section 7.2.4.

Table 3 describes how data will be categorized into visit windows:

Table 3: Analysis Visit Windows

Visit Number	Visit Day/Month	Visit Window for Analysis
1	DBP Day 0	Study Days -28-1
2*	DBP Day 7	Study Days 2-10
3	DBP Day 14	Study Days 11-22
4	DBP Day 30	Study Days 23-38
5	DBP Day 45	Study Days 39-53
6	DBP Day 60	Study Days 54-76
7a/7b	DBP Day 90/OLP Day 0	Study Days 77-98
8	OLP Month 3 (Day 180)	[OLP start day+1]+90±14
9	OLP Month 12 (Day 450)	[OLP start day+1]+365±14
10	OLP Month 24 (Day 810)	[OLP start day+1]+730±14

* Visit 2 (D7) can be a site visit, a home visit or a phone call
For OLP the start day for analysis is the day of allocation of medication for OLP (as recorded in the eCRF), or, where OLP was allocated before EDBP, the date of last use of gel at EDBP plus the number of days between dressing changes as recorded in the CRF at EDBP will be used. For patients withdrawn during DBP that proceed to OLP without completing DBP, visit windows for analysis will also be derived according OLP start day.

If a patient has multiple visits in the same visit window, the visit closest to the scheduled visit day will be used. If two visits are equidistant to the scheduled visit day, the earlier of the two values will be used. However, for the primary endpoint (proportion of patients with first complete closure of EB target wound within 45±7 days), if there is more than one visit within the assigned visit window and the first complete EB target wound closure occurred at any of them, it would count as wound closure at that visit.

For time to event analyses, the actual value of the study day will be used for calculating the time to event.

7.5. POOLING OF CENTRES

Due to the large number of centres and small number of patients/centres, centres are not pooled.

7.6. LEVEL OF SIGNIFICANCE, MULTIPLE COMPARISONS AND MULTIPLICITY

The overall level of significance for the primary endpoint analysis is 0.05 (two-sided). At the final analysis, the primary endpoint is tested at the 5% significance level. If the primary analysis is statistically significant, the confirmatory testing approach continues hierarchically with statistical testing of the key secondary endpoints at the 5% significance level (see Section 9.3 for more details).

The Cui, Hung, Wang (CHW) weighted test-statistic for sample size re-estimation does not require an adjustment of the significance level as the IA is for sample size re-estimation only and does not allow for early stopping due to early efficacy.

All further analyses are considered as non-confirmatory and descriptive only.

8. DEMOGRAPHICS, OTHER BASELINE CHARACTERISTICS AND MEDICATION

8.1. PATIENT DISPOSITION

The following patient dispositions are listed for all enrolled patients: informed consent date (including optional informed consent for collection of blood samples for betulin analysis and for genetic testing to determine EB subtype), patient eligibility (inclusion and exclusion criteria not met), randomisation/screen failure date and DBP and OLP completion status.

Number of patients enrolled, randomised, who completed or discontinued treatment (during DBP or OLP) and the study (DBP and OLP) are also summarized within all enrolled patients. Reasons for study discontinuation will be summarized in a separate table.

All individual home, site, and phone visits are listed with visit dates. The number and percentage of patients will be summarised within the SAF by visit made and related type of visit (home visit or site visit) for each study phase.

The number and percentage of patients included in each of the analysis sets and the reasons for exclusion from each of the analysis sets are presented.

8.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age, gender, ethnicity, Fitzpatrick skin type (Fitzpatrick 1988), height (cm) and weight (kg) are recorded at baseline.

Baseline characteristics are defined as all results of the examinations performed prior to the first Oleogel-S10 or vehicle administration at the First Study Treatment. These include summaries of EB subtype and EB target wound selection. See Section 7.2.3 for the definition of baseline.

Age is categorised as follows:

- Young Children (<4 years): patients < 4 years of age
- Children (4-11 years): patients >= 4 years of age and < 12 years of age
- Adolescents (12-17 years): patients >= 12 years of age and < 18 years of age
- Adults (>=18 years): patients >= 18 years of age

The Body Mass Index (BMI) is calculated as follows: BMI (kg/m^2) = Weight (kg)/[Height$(m)^2$].

Demographics and other baseline characteristics are listed and summarised in the SAF, with descriptive statistics for continuous variables and by absolute and relative frequencies for categorical variables.

8.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

The investigator asks the patient and/or his/her legal representative(s) for the patients' general and disease-specific medical history and current medical conditions.

The investigator records the EB subtype as well as the date and method of diagnosis (e.g., clinical diagnosis only, genetic analysis, immunofluorescence mapping or transmission electron microscopy). These data are summarized and listed. If prior genetic confirmation of EB subtype is not available for the patient, the patient may sign the optional consent for genetic testing to confirm EB subtype.

Medical history is coded by the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher, and sorted alphabetically by system organ class (SOC) and preferred term (PT). All data are summarized and listed.

8.4. MEDICATION

Prior medication is defined as any medication taken prior to the date of First Study Treatment. Concomitant medications are defined as medications with a start date on or after the date of the First Study Treatment or a stop date on or after the date of the First Study Treatment. During the DBP and OLP, all concomitant medications are recorded. Prior and concomitant medications are coded by the world health organization drug dictionary (WHO-DD) Version B3 Mar-2020 or higher.

Prior and concomitant medications are listed and summarised separately by Anatomic Group (Anatomical therapeutic chemical classification [ATC] level 1), ATC level 4, and WHO-DD PT. For concomitant medications, summary tables are presented separately for the DBP and the OLP. Medications starting during the DBP (between baseline DBP D0 and date of first study treatment of the OLP exclusive) are presented for DBP only and medications starting on or after the first study treatment of the OLP are presented for the OLP. An additional table will be provided with all concomitant medications throughout the study.

8.5. DRUG ACCOUNTABILITY, EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Study medication is administered and Standard of Care non-adhesive wound dressings are applied as described in Protocol sections 6.3 and 7, respectively, for the DBP until the end of treatment at D90±7 and in the OLP until the end of treatment at M24±14 days.

All data regarding the dressing change, study medication administration and the return of study medication are listed by visit and summarised by study phase in the SAF.

For each kit, the amount of study medication used is derived in grams (g) as follows:

Amount of medication used = Weight of total kit – Weight of used kit

With the “weight of total kit” as a standard value = 2,230 grams, and the “weight of used kit” as recorded in the eCRF.

Both the amount of medication used and unused is derived for each visit as the sum of the weights for all kits. To note that the kit weighting was only introduced starting from Protocol Version 3 and thus missing data are expected for administrations prior to the date when Protocol Version 3 was signed.

The allocation of the study medication at randomisation, during the DBP and for the OLP is only listed for the SAF.

For each study phase, extent of exposure is obtained as:

Treatment duration (days) = treatment end date – treatment start date +1

Actual extent of exposure is also calculated by subtracting the sum of treatment interruption durations from the above treatment duration formula, where the duration of each treatment interruption is obtained as:

Interruption duration (days) = interruption end date – interruption start date +1

Treatment compliance is calculated as follows:

Treatment compliance = actual treatment duration in days / treatment duration in days * 100

Treatment durations and compliance are summarised and listed separately by study phase.

For these two calculations (treatment compliance and interruption duration) only the interruptions on the target wound will be considered. If the reason for dose interruption is recorded as “wound closure” in the eCRF, this will not be considered for the calculation of interruption duration.

The overall treatment duration and compliance will be presented as well as the duration and compliance in relation to adverse events (which will be derived considering only “reasons for dose interruption” due to adverse events as recorded in the eCRF).

9. EFFICACY

9.1. EFFICACY ASSESSMENTS

The following efficacy assessments are performed for both the DBP and the OLP. All data are summarised and listed by visit.

9.1.1. Clinical Assessment and Photography of EB Target Wound and Other Wounds

The primary efficacy assessment of the EB target wound for closure is made by the investigator at each site or home visit.

In addition, the investigator or delegated site study team member photo-documents the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system for blinded efficacy assessment by 2 independent expert assessors and a 3rd expert as the adjudicator for discordant assessments.

During screening, the investigator takes a baseline reference image of the EB target wound and all other wounds that match target wound criteria. At future visits, the investigator always refers to the baseline reference image to ensure that the correct wound is assessed. The baseline reference image(s) are uploaded to the wound documentation report and the results are recorded in the eCRF.

For assessments after baseline, ARANZ provides an external database with the following information for each wound: site, patient number, visit day, anatomical site, assessment date, assessment number, wound label, wound area (cm^2), area reduction (%), perimeter (mm), length (mm), width (mm), ruler measurement (mm) and wound state (open or closed). All data are summarised and listed.

The 3 independent expert assessors are trained on the use of the ARANZ Silhouette® system and each receives a unique user ID/password to access the system. Once wound measurements have been recorded by the site in the system, images will be assigned a computer-generated unique identifier, the images will be blinded to remove all information such as patient number, visit number, anatomical site, wound tracings and wound measurements and the order of the images will be randomised.

The 2 independent assessors will receive a list of images ready for assessment. They will log into the ARANZ Silhouette® system using their unique user ID/password – system access is limited to only the blinded images. The assessors will trace and measure each wound, assess if the wound is open or closed and record their measurements in the assessors-specific field within the system.

When all measurements have been entered in the system by each assessor, the data will be decoded to present side-by-side data for each wound. Where there is discord between the wound measurements between the two assessors the image(s) will be presented to the adjudicator for assessment. The adjudicator enters his/her measurement into a specific adjudicator field within the system. If there is still discord between the assessors and the adjudicator, a meeting will be convened to discuss the image(s) and to reach

consensus. The final agreed measurement will be entered in the system by the adjudicator. The expert photo evaluation data will be provided by ARANZ as an external database.

In a blinded data review meeting (BDRM) prior to final unblinding, the amount of available data regarding photography and patient-reported outcomes (Section 9.1.4) will be evaluated for D7±2 to decide if statistical analysis will be performed for that time point (note that the D7 visit can be a site visit, a home visit or a phone call).

9.1.2. Total Body Wound Burden

Total body wound burden is assessed clinically by the Investigator using Section I (Skin except for the anogenital region) of the EBDASI (Loh, Kim et al. 2014). The EBDASI activity (blistering/erosions/crusting) is scored from 0 to 10 in each of the 10 anatomical locations and recorded in the eCRF and a total activity score is derived. The 10 anatomical locations are: ears, face, neck, chest, abdomen, back, arms, hands, legs, and feet.

9.1.3. Body Surface Area Percentage

Body Surface Area Percentage (BSAP) of TBSA affected by EB partial thickness wounds is assessed clinically by the Investigator using a matrix based on the 'Lund and Browder' chart (Miminas 2007) which includes a weighting factor by age (see Figure 9 of the protocol). The "Regional BSAP" and "Total BSAP" percentages are recorded and derived (respectively) in the eCRF for each individual anatomical region. The anatomical regions are: head & neck, arms (upper, lower, and hands), trunk (anterior, posterior), legs (thighs, lower legs, and feet). An overall sum of all domains is also derived in the eCRF for the total BSAP.

9.1.4. Patient-reported Outcomes

Since a Health-related Quality of Life (HRQoL) instrument evaluating age-appropriate concepts for EB was not available and content validity was lacking in the majority of HRQoL measures (Mordin, Clark et al. 2012), the concepts 'pain', 'itch', 'impact of wounds on sleep', and the patient's satisfaction with treatment are assessed with concept-specific Patient-reported Outcome (PRO) instruments instead. For more details on the PRO and the sample questionnaires for their measurement, see Section 8 of the Protocol.

Itching is assessed with two tools: the 'Itch Man Scale' for patients ≥4 years and up to 13 years of age, and the 'Leuven Itch Scale' in patients ≥14 years of age. Due to the limited ability of patients <4 years to assess the intensity of itch, this subgroup of patients is excluded from these analyses.

Background pain (before wound dressing change) and procedural pain (due to wound dressing change) are rated with the Face, Legs, Activity, Cry, Consolability (FLACC) Pain Rating Scale for patients <4 years of age, and with the Wong-Baker FACES® Pain Rating Scale for patients ≥4 years of age.

9.1.4.1. 'Itch Man Scale'

In patients ≥4 years and up to 13 years of age, itching is assessed using the 'Itch Man Scale' (Morris, Murphy et al. 2012). The 'Itch Man Scale' is the only measure that specifically assesses itching in children, and is a validated itch assessment tool.

For each visit, the total score for the 'Itch Man Scale' is recorded in the eCRF.

9.1.4.2. 'Leuven Itch Scale'

In patients ≥14 years of age, itch is evaluated using the 'Leuven Itch Scale' (Haest, Casaer et al. 2011). The 'Leuven Itch Scale' is an instrument measuring all dimensions of the itch experience in the previous month including symptom occurrence (frequency, duration, severity, and circumstances), symptom distress, symptom management, symptom location, sensory perception of the symptom, and consequences of the symptom.

Patient answers to the questions for all dimensions are recorded in the eCRF. Using the recorded patient data, the methods below are followed to calculate subscale scores on 6 domains of interest (as suggested by Moons 2015). Only the questions indicated below are used for the calculation of the subscale scores.

All patient answers to all questions and the derived subscale scores per patient are listed, including the standard deviation of each subscale score. Summary tables present descriptive statistics of the subscale scores by visit and study phase.

9.1.4.2.1. Itch Frequency subscore

For each visit, the Frequency subscore is obtained with the item *"How often did you experience itch in the past month?"* in Question 1 of the scale.

Recorded answers are transformed as follows: 'Never' = 0; 'Rarely (1 to a few times per month)' = 25; 'Sometimes (1 to a few times per week)' = 50; 'Often (1 to a few times per day)' = 75; and 'Always' = 100.

The second item in Question 1 (i.e., *"If 'never', why did the itch not occur/return?"*) are not used for the calculation of the Frequency subscore.

9.1.4.2.2. Itch Duration subscore

For each visit where the Frequency subscore is greater than 0, the Duration subscore is obtained with the item *"In the past month, how long, on average, did your itching episode last?"* in Question 2 of the scale.

Recorded answers are transformed as follows: 'Between 0 and 30 min' = 0; 'Between 30 and 60 min' = 33.33; 'Between 1 and 2 hours' = 66.66; and 'More than 2 hours' = 100.

9.1.4.2.3. Itch Severity subscore

For each visit where the Frequency subscore is greater than 0, the Severity subscore is obtained with the item *"In the past month, how bad was the itching you have been experiencing?"* in Question 5 of the scale.

Question 5 is measured using a Visual Assessment Scale (VAS) of 10 cm length. Since some sites were erroneously provided with a VAS with a shorter length than expected, the itch severity subscore is derived in two different ways:

1. Using original responses: Recorded answers are transformed by multiplying the record by 10, e.g. a recorded answer of '5' is transformed as '50'
2. Using scaled-up responses (for sensitivity analysis): values recorded with an incorrectly sized scale are converted to a common scale and multiplied by 10 as: Scaled-up itch severity subscore = [(recorded answer*10)/actual VAS length]*10

The actual VAS length will be provided to the programming team in an external spreadsheet by the study clinical team.

9.1.4.2.4. Itch Consequences subscore

For each visit where the Frequency subscore is greater than 0, the Consequences subscore is obtained with the first 11 items (i.e., items a, b, c, d, e, f, g, h, i, j and k) of Question 8 of the scale *"In the past month, what were the consequences of your itching?"*. Item l *"other consequences"* is not used to derive this subscore.

The recorded answers in the first 11 items of Question 8 are transformed as follows: 'Never' = 0; 'Rarely' = 25; 'Sometimes' = 50; 'Often' = 75; and 'Always' = 100. The by visit Consequences subscore is the average of the 11 items for Question 8.

9.1.4.2.5. Itch Distress subscore

For each visit where the Frequency subscore is greater than 0, the Distress subscore is obtained with the item *"In the past month, how distressing was your itching?"* in Question 10 of the scale.

Similar to Question 5, Question 10 is also measured using a VAS of 10 cm length. Since some sites were erroneously provided with a shorter VAS than expected, the itch Distress subscore is derived in two different ways:

1. Using original responses: Recorded answers are transformed by multiplying the record by 10, e.g. a recorded answer of '5' is transformed to '50'
2. Using scaled-up responses (for sensitivity analysis): values recorded with an incorrectly sized scale are converted to a common scale and multiplied by 10 as:

Scaled-up itch distress subscore = [(recorded answer*10)/actual VAS length]*10

The actual VAS length will be provided to the programming team in an external spreadsheet by the study clinical team.

9.1.4.2.6. Itch Surface Area subscore

For each visit where the Frequency subscore is greater than 0, the Surface Area subscore is obtained with all the 13 items of Question 11 of the scale, i.e. *"In the past month, which parts of your body itched? (Shade the area(s) which itched.)"*.

For each item selected (indicating that itching was present in the corresponding body area), a value of 100 is assigned to that item. For each item not selected, 0 will be assigned. The Surface Area subscore is the average of the 13 items for Question 11.

9.1.4.3. 'Face, Legs, Activity, Cry, Consolability' (FLACC) Pain Rating Scale

In patients <4 years of age, the investigator or delegated site study team member uses the Face, Legs, Activity, Cry, Consolability (FLACC) pain rating scale for assessing "background" pain before wound dressing change and "procedural" pain due to wound dressing change (Merkel, Voepel-Lewis et al. 1997).

The FLACC scale measures the background and procedural pain in 5 different categories, and a total score is derived in the eCRF.

9.1.4.4. 'Wong-Baker FACES®' Pain Rating Scale

In patients ≥4 years of age, the 'Wong-Baker FACES® Pain Rating Scale' is used for assessing "background" pain before wound dressing change and "procedural" pain due to wound dressing change (Wong-Baker 2015).

The total score for the 'Wong-Baker FACES® Pain Rating Scale' is recorded in the eCRF.

9.1.4.5. Impact of Wounds on Sleep

In patients ≥14 years of age, the site study team member asks before the visit's wound dressing change: "Have the wounds affected your sleep within the last 7 days" using an 11-point Likert scale ('Not at all' = 0, 'Very much' = 10) (Blome, Baade et al. 2014).

9.1.4.6. Days Missed from School or Work

A site study team member asks the patient (in patients ≥14 years of age) or a parent (in patients <14 years of age) whether he/she has missed any days from school or from work due to EB in the last 14 days (D0) or since the last visit (days missed to attend study visits are not counted).

For each study phase, the cumulative number of days missed are derived as the sum of the days reported at all visits between the first and the last study treatment dates.

9.1.4.7. Treatment Satisfaction Questionnaire for Medication (TSQM)

A site study team member asks the patient (in patients ≥14 years of age) whether he/she was satisfied with the treatment using the abbreviated Treatment Satisfaction

Questionnaire for Medication (TSQM) Version 9 (Bharmal, Payne et al. 2009). The questionnaire contains 9 questions and the overall satisfaction or dissatisfaction with the medication is measured by Question 9.

9.1.4.8. Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB)

The Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) is a combined score that contains clinician- and patient-derived items. This instrument was proposed by Schwieger-Briel et. al. (2015) and the combined scores allow differentiation between EB subtypes and degrees of severity (Schwieger-Briel et al. 2015).

For the clinician items 5 domains are evaluated (skin involvement, mucosal involvement, internal organ involvement, laboratory abnormalities, and complications/procedures). Each item contains several questions that are used to obtain an item "score", that allows the calculation of a "total clinician score" by adding all individual item scores. The maximum total clinician score is a value of 138.

For the patient items 7 domains are evaluated (pain, itch, essential functions, sleeping, daily activities, mood and impact). Each item contains questions that are used to obtain an item "score", that allows the calculation of a "total patient score" by adding all individual item scores. The maximum total patient score is a value of 120.

Item scores, Clinician and patient scores as well as a total iscorEB score are recorded and derived in the eCRF.

9.1.4.9. EQ-5D

EuroQol 5 Dimensions (EQ-5D) is a standardized instrument developed by the EuroQol Group (euroqol.org) as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. For this study, the EQ-5D-Y, the Proxy version of the EQ-5D-Y:1 and the EQ-5D-5L with 5 levels of severity are assessed as applicable depending on the patient's age at D0 (Herdman et al 2013, Wille et al 2010). The Proxy version of the EQ-5D-Y:1 is used for patients < 4 years at D0 and is completed by the patient's parent/caregiver - the proxy will not answer on behalf of the child, but rather rate the child's health status as the proxy sees it; the EQ-5D-Y is used for patients aged 8 to 15 years at D0 and the EQ-5D-5L is used for patients > 16 years at D0.

All questionnaires assess several dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with a multiple choice question (3 possible choices for the EQ-5D-Y and the Proxy version of the EQ-5D-Y:1 and 5 possible choices for the EQ-5D-5L.). An overall score between 0 (worst possible) and 100 (best possible) is also recorded to describe how good or bad the health of the patient is on the day of the assessment.

All questions to assess individual dimensions and the overall score are recorded in the eCRF.

9.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

This study is a double-blind, randomised trial with a control gel to show superiority of Oleogel-S10 as compared to the control gel in the promotion of healing of EB partial thickness wounds. Note that vehicle and control gel are used interchangeably throughout this document; however control gel is the preferred term to use in the analyses for all TLFs.

The analysis of the primary efficacy endpoint is performed on the FAS as follows and is presented in the CSR (DBP):

The proportion of patients with first complete closure of the EB target wound within 45±7 days based on clinical assessment by the investigator is compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB subtype and target wound size class. The hypothesis is defined in terms of the common odds ratio (OR). The OR is calculated from the proportions $p_{Oleogel\text{-}S10}$ and $p_{Vehicle}$ of patients with first complete closure of the wound within 45±7 days in the Oleogel-S10 treatment group and the vehicle group, respectively: $OR = (p_{Oleogel\text{-}S10}/(1-p_{Oleogel\text{-}S10})) / (p_{Vehicle}/(1-p_{Vehicle}))$. The respective null ($H_0$) and alternate ($H_1$) hypotheses are:

$$H_0: OR = 1 \text{ versus } H_1: OR \neq 1.$$

The first complete closure of the EB target wound is assessed by the investigator within 45±7 days of treatment. Thus, the target wound is deemed as having a first complete closure only if the "Clinical Assessment" states that the wound has closed.

The analysis of the primary efficacy endpoint considers missing data with regard to wound closures as failures.

The unblinded IA included a sample size re-estimation using the CHW approach with a weighted test statistic, a statistical analysis of the primary efficacy endpoint using the stratified CMH test and a computation of the conditional power to check for futility (see Section 11 "IDMC and Interim Analysis" and the separate document "Sample Size Report for Re-estimation" for more details).

Since the IDMC deemed it necessary to increase the sample size after the IA, the final statistical analysis of the primary efficacy endpoint will be performed based on the CHW approach to adjust the estimates provided by the CMH test.

9.3. ANALYSIS OF KEY SECONDARY EFFICACY ENDPOINTS

The overall level of significance for the primary endpoint analysis is 0.05 (two-sided). If the primary analysis of the primary efficacy endpoint demonstrates superiority at the 5% significance level, hierarchical confirmatory testing of the key secondary endpoints is performed on the FAS as described below and is presented in the CSR (DBP). If the primary efficacy endpoint does not show superiority at the 5% significance level, the analysis of the key secondary endpoints is still presented, albeit only as non-confirmatory and descriptive:

1. Time to first complete closure of the EB target wound as evidenced by clinical assessment until the EDBP at 90±7 days of treatment.

Time to first complete closure of the EB target wound as evidenced by clinical assessment is derived as the difference in days between the date of the clinical assessment of the wound closure where it was indicated that the target wound closed and DBP D0 + 1 day. If wound closure does not occur prior to the EDBP, time will be censored to the EDBP visit date.

This analysis is performed using the non-stratified log-rank test.

2. Proportion of patients with first complete closure of the EB target wound within 90±7 days based on clinical assessment by the investigator.

   This analysis is performed using the stratified CMH test.

3. The incidence of wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection).

   A wound infection event is counted for the patient if one of the following occurs:

   - the patient has a recorded AE with lowest level term (LLT) suggesting a wound infection e.g.: Wound infection, Wound complication, Wound odour, Superinfection, Infection Pseudomonas aeruginosa, Staphylococcal infection
   - the patient has recorded concomitant antibiotic(s) with:
     - Route recorded as one of the following: Topical, Oral, Other, Intravenous; and
     - Indication suggesting the treatment of wound infection, for example containing one of the following, but not limited to: wound, infection, inflammation, staph, pseud, strep, bact, antiseptic, disinfection, wash. A complete medical review will be made prior to database lock and the final medication list will be provided to the programming team.

   The incidence rates of wound infection are calculated as:

   Incidence rate = total number of patients with wound infection / total number of patients.

   Incidence rates of target wound infection between treatments are compared using a CMH test considering the strata of EB subtype and target wound size class.

   Summary statistics for the incidence rates of all wound types will also be presented.

4. The maximum severity of target wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection).

   The maximum severity is evaluated as follows: if a patient has wound infection event indicated by an AE as described above, the maximum severity of the AE is compared between treatments using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

Summary statistics for the maximum severity of all wound types will also be presented.

5. Change from baseline (DBP D0) in total body wound burden as evidenced by clinical assessment using Section I (assessment of the skin activity score except for the anogenital region) of the 'EB Disease Activity and Scarring Index' (EBDASI) at D90±7.

   The change from baseline is calculated for the total wound burden score as well as for the separate subscores and are analysed using an analysis of covariance (ANCOVA) with treatment group, EB subtype, and target wound size class as fixed effects and EBDASI score (overall or subscore as appropriate) at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.

   For confirmatory testing, only the change from baseline in the overall score are tested and if significant, the hierarchy continues with the next key secondary endpoint.

6. Change from baseline (DBP D0) in itching using the 'Itch Man Scale' in patients ≥ 4 years and up to 13 years of age and the 'Leuven Itch Scale' in patients ≥ 14 years of age, before wound dressing changes at D90±7.

   The changes from baseline between treatments are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

   For confirmatory testing, the hierarchy tests both the 'Itch Man Scale' and the 'Leuven Itch Scale' separately.

9.4. SENSITIVITY, SUPPORTIVE AND SUBGROUP ANALYSES

9.4.1. Sensitivity and Supportive Analyses for Primary Efficacy Endpoint

1. In addition to the analysis of the primary efficacy endpoint described above using the FAS, the analysis is repeated similarly using the CAS and the PPS as sensitivity analyses. For these analyses the adjustment of the CMH estimates with CHW is not required.
2. An additional analysis is performed using the CMH test on the FAS with the first complete wound closure evaluation based on the clinical assessment by the investigator and confirmed by a second observation after 7 days [+2 days] at the confirmation of complete closure (CCC) visit. The second observation is provided by the Investigator's assessment either at a CCC site visit or by assessment of the photograph obtained at a CCC home visit. For this analysis, the first wound closure will only be considered a success if both the clinical assessment and the second observation assess the wound as closed.
3. Additionally, a Fisher's exact test and a Pearson's chi-square test for comparison between treatment groups without consideration of any stratification is provided for the overall difference in proportions of first wound closure within D45±7, as

well as the 95% CI for the difference between the proportions. This analysis will be repeated on the proportions of first wound closure within D45±7 confirmed by a second observation after 7 days [+2 days] at the CCC visit (the second observation is provided by the Investigator's assessment either at a CCC site visit or by assessment of the photograph obtained at a CCC home visit).

4. Further potential confounding factors are investigated by a logistic regression model with consideration of EB subtypes, target wound size class, and additional baseline factors. This analysis is provided only for the FAS.
5. The effect of "worst-case" imputation for missing values with regard to wound closure is investigated: A patient in the Oleogel-S10 group with missing data is defined as a failure, while a patient in the vehicle group with missing data is defined as a success. This analysis is performed similarly as the primary efficacy analysis only for the FAS.
6. If the analysis of the primary efficacy endpoint significantly favours the Oleogel-S10 group, a sensitivity analysis based on multiple imputation (MI) is conducted using the tipping point approach to assess the departures from missing at random (MAR) to missing not at random (MNAR) assumptions only for the FAS.

   As first step, a monotone missing pattern, *i.e.* missingness from early treatment discontinuation onwards and not due to an in-between missed efficacy assessment, is created by imputing under the MAR assumption using the stochastic Markov Chain Monte Carlo (MCMC) method. Monotone missing patterns are then imputed using a sequential (visit-by-visit) regression model with a discriminant function.

   The distribution of imputed responses in the Oleogel-S10 group under the MAR assumption is assumed worse than for the control group, i.e. non-closure of the EB target wound. Variations in the assumptions for the MI are examined to adjust the imputed values until the statistical significance is lost (i.e., the p-value is greater than 0.05).
7. The CMH test is repeated using the FAS albeit considering complete closure of wounds at D45±7 instead of the first occurrence of complete closure within D45±7.
8. The CMH test, Fisher's exact test and the chi square test without consideration of strata are repeated on PPS and CAS.
9. As a supportive analysis of the primary efficacy endpoint, among the patients with a first closure of the EB target wound at a visit prior to D45±7, the proportion of patients with no re-opening by D45±7 will be compared using the stratified CMH test.
10. The CMH test using the FAS is repeated stratified by the type of wound dressing used during the clinical assessment of first wound closure within D45±7 days (permitted/non-permitted dressings/contact layers as recorded in the eCRF). A final medical review of the dressings/contact layers will be performed prior to database lock and the list of non-permitted dressings/contact layers will be provided to the programming team. A list is also presented in Appendix 1.

11. To assess the impact in the clinical assessment of wound closure due to COVID-19, an additional analysis will be performed: a patient with a clinical assessment that was not performed as indicated in the protocol due to COVID-19 (e.g., visit was not performed during scheduled window or performed using a different method (e.g. phone/ video/ home visit)) is defined as a failure. This analysis is performed with the CMH test stratified by EB subtype and target wound size only for the FAS.
12. An additional analysis will be provided to examine the time to first complete closure of the EB target wound as evidenced by clinical assessment within D45±7. Time to first complete closure is derived as the difference in days between the date of the clinical assessment of the wound closure where it was indicated that the target wound closed and DBP D0 + 1 day. If wound closure does not occur prior to study D45±7, time will be censored to D45±7 visit date. This analysis is performed using the non-stratified log-rank test. A Kaplan-Meier plot will also be provided

9.4.2. Sensitivity and Supportive Analyses for Key Secondary Efficacy Endpoints

1. The non-stratified log-rank test is repeated on the CAS and PPS. These supportive analyses are performed regardless of the significance of the corresponding key secondary efficacy endpoint.
2. Additionally, the stratified log-rank test with consideration of EB subtypes (based on actual data) as strata is performed on the FAS. Kaplan-Meier plots for this analysis are also provided.
3. Further potential confounding factors are investigated by a Cox regression model on the FAS with adjusting for EB subtypes (based on actual data), target wound size class, and additional baseline factors (e.g., age, gender, haemoglobin level, renal function and serum albumin level). The exact baseline factors were defined as permitted/ non-permitted dressings within Day 45, anaemia, and nutritional status albumin before the database was locked and this is documented in the minutes of the blind data review meeting.
4. The analysis of the incidence of wound infection between baseline (DBP D0) and D90±7 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection) is repeated among the subgroup of patients who have treated all wounds with study medication in the majority of visit assessments (e.g., if the patient answered the question "was gel used in all wounds" five times, at least three "yes" are necessary to be included in the subgroup; if the same number of "yes" and "no" is available then the patient is excluded from the subgroup). This analysis will also be performed for the subset of those patients with wound infections which have been bacteriologically confirmed. The bacteriological confirmation is added to the corresponding AE verbatim as recorded in the eCRF. A complete medical review of

the swab results and corresponding AEs will be performed prior to database lock and the final list will be provided to the programming team.

5. Due to the presence of some sites using a shorter VAS than expected, the summary statistics for the Leuven Itch Scale by visit and study phase is repeated as a supportive analysis to reassure about the confidence of the results of the key secondary analysis by using the scaled-up versions of the itch severity subscore and distress subscore.

9.4.3. Subgroup analyses for Primary Efficacy Endpoint and First Key Secondary Efficacy Endpoint (Time to First Complete Closure of the EB Target Wound)

This section describes subgroup analyses to be performed for the primary efficacy endpoint (i.e., proportion of patients with first complete closure of the EB target wound within 45±7 days based on clinical assessment by the investigator) and the first key secondary efficacy endpoint (i.e., time to first complete closure of the EB target wound).

The stratification factors used in randomisation are subgroups of interest. These are the 6 different combinations between 2 EB subtypes and the size of target wound (cm^2): JEB/Kindler 10 to <20, JEB/Kindler 20 to <30, JEB/Kindler 30 to 50, DEB 10 to <20, DEB 20 to <30, and DEB 30 to 50.

In addition to the randomisation subgroups, the following subgroups are also evaluated (all subgroup definitions based on the FAS):

- EB subtype [JEB, DDEB, RDEB, Kindler] (patients with EBS will be excluded from the subgroup analysis)
- Size of target wound [10 to <20 cm^2, 20 to <30 cm^2, 30 to 50 cm^2]
- Age group [Young Children (<4 years), Children (4-11 years), Adolescents (12-17 years), Adults (>=18 years)]
- Gender [Female vs Male]
- Race [White, Black or African American, Asian, Other]
- Contact layer/dressing type based on the duration of use before first wound closure within D45±7 days (for primary efficacy) or up to D90±7 days (for key secondary efficacy) [permitted vs non-permitted]. The duration of use until first wound closure of each contact layer/dressing type will be calculated between visits based on the visit day, and the type with the longest duration will be selected. If the duration of both types is equal then type 'non-permitted' will be assigned. If there is no wound closure the duration will be calculated until D45±7 or D90±7. If the patient is withdrawn then the duration will be calculated until day of withdrawal. A list will be provided to the programming team to categorize each contact layer/dressing entry recorded in the eCRF.
- Baseline Nutritional status (categorized as 1st tertile, 2nd tertile, 3rd tertile based on the baseline distribution of serum albumin level in all patients in the FAS who provide a baseline value)

- Baseline Anaemia (categorized as 1st tertile, 2nd tertile, 3rd tertile based on the baseline distribution of haemoglobin in all patients in the FAS who provide a baseline value)
- Baseline Renal Function (categorized as 1st tertile, 2nd tertile, 3rd tertile based on the baseline distribution of estimate glomerular filtration rate (eGFR) in all patients in the FAS who provide a baseline value in creatinine)

If deemed necessary for a meaningful analysis, categories might be further combined together to reduce the number of subgroups.

eGFR values will be calculated for paediatric patients (0 to <18 years old) following the derivation at: http://www-users.med.cornell.edu/~spon/picu/calc/crclschw.htm; and for adults (>= 18 years old), following the derivation of Chronic Kidney Disease Epidemiology Collaboration creatinine equation (2009) as recommended by the National Kidney Foundation.

For paediatric patients (age < 18 years) the eGFR is calculated as:

$$eGFR = (Pconstant^* Height)/CrSerum,$$

where Pconstant is the proportionality constant equal to 0.45 (for Infants < 1 year) or 0.55 (for Child >= 1 year and < 12 years) or 0.7 (for Adolescent >= 12 years and < 18 years), Height is given in cm, and CrSerum is the observed Creatinine (Biochemistry assessment) in mg/dL.

For adult patients (age >= 18 years) the eGFR is calculated as:

$$eGFR= 141 * \min(CrSerum/Pconstant,1)^{alpha} * \max(CrSerum/Pconstant,1)^{-1.209} * 0.993^{Age} * 1.018 \text{ [if female]} * 1.159 \text{ [if black]} ,$$

where Pconstant is equal to 0.7 (females) or 0.9 (males), alpha is equal to -0.329 (females) or -0.411 (males), Age is given in years, min indicates the minimum and max indicates the maximum, and CrSerum is the assessed Creatinine value (Biochemistry assessment) converted to mg/dL.

In case the patients does not have a Creatinine assessment measured in mg/dL as the original result, the original result will be converted to mg/dL before calculating the eGFR.

A forest plot of the odds ratio obtained from the following subgroup analysis will also be presented: EB subtype, size of target wound, age, gender, race, baseline nutritional status and baseline Anemia.]

9.5. ANALYSIS OF ADDITIONAL DBP SECONDARY EFFICACY ENDPOINTS

These additional secondary efficacy endpoints are analysed in the FAS and summarised by visit unless stated otherwise:

1. The proportion of patients with first complete closure of the EB target wound at D14±5, D30±7 and D60±7 based on clinical assessment by the investigator is analysed using the stratified CMH test.
2. The proportion of patients with first complete closure of the EB target wound at D7±2, D14±5, D30±7, D45±7, D60±7 and D90±7 based on patient assessment is analysed using the stratified CMH test.
3. The proportion of patients with first complete closure of the EB target wound at D7±2, D14±5, D30±7, D45±7, D60±7 and D90±7 based on blinded evaluation of photographs is analysed using the stratified CMH test.
4. As an additional analysis, the proportion of patients with first complete closure of at least one non-target EB partial thickness wound (i.e., additional wounds) is analysed using the stratified CMH test. The complete closure is based on the clinical assessment by the investigator. This analysis is only applicable for patients that have an additional wound identified.
5. The percentage change from baseline (DBP D0) in EB target wound size as evidenced by blinded evaluation of photographs taken at D7±2, D14±5, D30±7, D45±7, D60±7, and D90±7, calculated as follows:

   Percentage change = ((wound size at visit x – wound size at baseline) / wound size at baseline) *100%, with the "wound size" given by the "Area (cm^2)" as recorded by the Aranz Silhouette system.

   The percentage change is analysed for each visit using an ANCOVA with treatment group and EB subtype as fixed effects and size of target wound at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.

   A boxplot showing the percentage change from baseline in EB target wound size (i.e., Area) for all time points analysed, additionally including descriptive statistics for the mean and standard deviation, are also presented.
6. As an additional analysis, the average percentage change from baseline in the size of all non-target EB partial thickness wounds (i.e., additional wounds) is analysed similarly to item 5 above.
7. As an additional analysis, the percentage change from baseline in size for the EB target wound is compared between treatments using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype (van Elteren test).

8. As an additional analysis, the average percentage change from baseline in size of all non-target EB wounds (i.e., additional wounds) is compared between treatments using a 2-sided Wilcoxon Rank sum test stratified by EB subtype (van Elteren test).
9. The change from baseline (DBP D0) in total body wound burden is evaluated by clinical assessment using Section I of the EBDASI at D30±7 and D60±7. The changes from baseline for each visit is calculated for the EBDASI scores (as derived in the eCRF) and is analysed using an ANCOVA with treatment group, EB subtype, and target wound size at baseline as fixed effects and EBDASI total activity score at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups is calculated.
10. The change from baseline (DBP D0) in BSAP of TBSA affected by EB partial thickness wounds is evaluated by clinical assessment based on the 'Lund and Browder' chart at D30±7, D60±7, and D90±7, calculated for the overall total BSAP and individual scores (as derived in the eCRF). The changes from baseline for each visit is analysed using an ANCOVA with treatment group, EB subtype, and target wound size at baseline as fixed effects, and the overall BSAP baseline score as a covariate. The 95% CIs for the difference in least squares means between treatment groups is calculated.
11. The change from baseline (DBP D0) in "background" pain is evaluated using the FLACC scale in patients <4 years of age and the 'Wong-Baker FACES® Pain Rating Scale' in patients ≥4 years of age before wound dressing changes at D7±2, D14±5, D30±7, D45±7, D60±7, D90±7. Three separate analyses are performed:
    - Total score of FLACC scale (as derived in eCRF) analysed independently
    - Total score of 'Wong-Baker FACES® Pain Rating Scale' (as recorded in eCRF) analysed independently
    - An analysis combining both groups of patients above. For this purpose, the 'Wong-Baker FACES® Pain Rating Scale' scores are transformed to allow for a comparison with the FLACC scores as follows: score values {0,2} are transformed to 0; score values {4,6} are transformed to 1; and score values {8,10} are transformed to 2.

    Treatments are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
12. The change from baseline (DBP D0) in "procedural" pain is evaluated using the FLACC scale in patients <4 years of age and the '*Wong-Baker FACES® Pain Rating Scale*' in patients ≥4 years of age after wound dressing changes at D7±2, D14±5, D30±7, D45±7, D60±7, D90±7. Three separate analyses are performed:
    - Total score of FLACC scale (as derived in eCRF) analysed independently
    - Total score of '*Wong-Baker FACES® Pain Rating Scale*' (as recorded in eCRF) analysed independently
    - An analysis after combining both groups of patients. For this purpose, scores are transformed as for the analysis of "background" pain.

Treatments are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

13. The change from baseline (DBP D0) in itching is evaluated using the '*Itch Man Scale*' or the '*Leuven Itch Scale*' before wound dressing changes at D7±2, D30±7 and D60±7. Two different analyses are performed:
    - 'Itch Man Scale' total score (as recorded in the eCRF) analysed independently
    - '*Leuven Itch Scale*' analysed independently. For this analysis, the change from baseline of all the 6 derived subscale scores is obtained.

    Treatments are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
14. The change from baseline (DBP D0) in the impact of wounds on sleep (in patients ≥14 years of age) is evaluated using 11-point Likert scales at D7±2, D30±7, D60±7, and D90±7. This is analysed using an ANCOVA with treatment group and EB subtype as fixed effects and the score of the impact of wounds on sleep evaluation at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.
15. The number of days missed from school or from work is evaluated. All days missed from school or from work are added up for the entire DBP (D0 to D90±7). Treatment groups are compared descriptively. Baseline data are summarised; no change from baseline are calculated.
16. The treatment satisfaction (in patients ≥14 years of age) is evaluated using the TSQM, Version 9 before wound dressing changes at D7±2, D30±7, D60±7, and D90±7. The overall treatment satisfaction or dissatisfaction is measured by Question 9 of this scale. The overall score is analysed using an ANCOVA with treatment group and EB subtype as fixed effects, and TSQM overall score at Day 7 as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.

9.6. ANALYSIS OF OLP EFFICACY ENDPOINTS

The efficacy analyses for the complete OLP will be performed at the EOLP (i.e., for the CSR (OLP)).

The OLP includes patients who have already received Oleogel-S10 for up to 90 days during the DBP and will continue to receive Oleogel-S10 during the OLP and patients who received control gel for up to 90 days during the DBP who then receive active Oleogel-S10 treatment during the OLP. Note that for the control patients, the time

period up to M3±14 days of the OLP mirrors baseline (D0) to D90±7 days of the DBP in those patients who were randomised to Oleogel-S10.

Summary tables for OLP efficacy endpoints will include summary statistics by visit for the complete study. If changes from baseline are applicable, tables will include change from OLP baseline (OLP DO) only.

The OLP efficacy endpoints are analysed using the FAS and summarised by visit unless stated otherwise as described below. These analyses are presented in the CSR (OLP):

1. The maximum severity of wound infection between OLP baseline (OLP D0) and M24±14 days as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection).

   The maximum severity is evaluated as follows: if a patient has a wound infection event indicated by an AE, the maximum severity of the AE is compared between treatments using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

2. For the subgroup of patients randomised to the control group who have unhealed target wounds at EDBP, the incidence of target wound infection (as evidenced by AEs and/or use of topical and/or systemic antibiotics [related to wound infection]) for the periods OLP baseline (OLP D0) through M3±14 days and DBP baseline (DBP D0) through D90±7 will be compared using a McNemar test.

3. The change from OLP baseline (OLP D0) in total body wound burden is evaluated by clinical assessment using Section I of the EBDASI at M3±14 days. The change from baseline for the total activity score and subscores (as derived in the eCRF) is analysed using an ANCOVA with treatment, EB subtypes, and target wound size at baseline OLP (OLP D0) as fixed effect terms, and the respective EBDASI baseline total activity score as covariate. The 95% CIs for the difference in least squares means between treatment groups referring to the group in the DBP are calculated.

4. The change from OLP baseline (OLP D0) in BSAP of TBSA affected by EB partial thickness wounds is evaluated by clinical assessment based on the '*Lund and Browder*' chart at M3±14 days, calculated for overall BSAP and domain scores (as derived in the eCRF). The changes from baseline in the overall total BSAP is analysed using an ANCOVA with treatment, EB subtype, and target wound size at baseline OLP (OLP D0) as fixed effect terms, and the respective baseline value of BSAP as covariate. The 95% CIs for the difference in least squares means between treatment groups referring to the group in the DBP are calculated.

5. The change from OLP baseline (OLP D0) in "background" pain is evaluated using the FLACC scale in patients <4 years of age and the '*Wong-Baker FACES® Pain Rating Scale*' in patients ≥4 years of age before wound dressing changes at M3±14 days. Three separate analyses are performed, similarly as for the DBP. Treatment groups referring to the group in the DBP are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

6. The change from OLP baseline (OLP D0) in "procedural" pain is evaluated using the FLACC scale in patients <4 years of age and the '*Wong-Baker FACES® Pain Rating Scale*' in patients ≥4 years of age after wound dressing changes at M3±14 days. Three separate analyses are performed, similarly as for the DBP. Treatment groups referring to the group in the DBP are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
7. The change from OLP baseline (OLP D0) in itching is evaluated using the '*Itch Man Scale*' or the '*Leuven Itch Scale*' before wound dressing changes at M3±14 days. Two different analyses are performed, similarly as for the DBP. Treatment groups referring to the group in the DBP are compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
8. The change from OLP baseline (OLP D0) in the impact of wounds on sleep (in patients ≥14 years of age) is evaluated using 11-point Likert scales at M3±14 days. This is analysed using an ANCOVA with treatment group referring to the group in the DBP and EB subtype as fixed effects and the score of the impact of wounds on sleep evaluation at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.
9. The number of days missed from school or from work is evaluated. Days missed from school or from work are added up for the 14-days preceding M3±14 days. Data for 14-day periods preceding DBP D0, D90±7 and M3±14 days are compared taking into account the treatment received during the DBP.
10. Treatment satisfaction (in patients ≥14 years of age) is evaluated using the TSQM, Version 9, before wound dressing changes at M3±14 days. The overall treatment satisfaction or dissatisfaction is measured by Question 9 of this scale. The overall score is analysed using an ANCOVA with treatment group referring to the group in the DBP and EB subtype as fixed effects and TSQM overall Score at baseline as a covariate. The 95% CIs for the difference in least squares means between treatment groups are calculated.
11. The following analyses will be performed using a paired t-test for:
    - total body wound burden evaluated by EBDASI,
    - BSAP of TBSA affected by EB partial thickness wounds,
    - "background" pain, "procedural" pain using FLACC Pain Rating Scale, the Wong-Baker FACES® Pain Rating Scale and a combination of both scales (similarly as discussed in Section 9.5.11)
    - itching using the Itch Man Scale or the Leuven Itch Scale,
    - the impact of wounds on sleep using the W-QoL Scale,
    - number of days missed from school or from work
    - and treatment satisfaction using the TSQM
        - For patients randomised to the control group, the change from OLP baseline (OLP D0) through M3±14 days and changes from DBP baseline (DBP D0) through D90±7 days will be compared

- For patients randomised to the Oleogel-S10 group, the changes from OLP baseline (OLP D0) through M3±14 days and changes from DBP baseline (DBP D0) through D90±7 days will be compared
- For all patients (regardless of treatment group), the changes from OLP baseline (OLP D0) through M12±14 days and change from OLP baseline through M24±14 days will be compared. Since the only assessments performed at M12±14 days and M24±14 days are total body wound burden evaluated by EBDASI and BSAP of TBSA affected by EB partial thickness wounds, this comparison is only applicable for these two assessments.

12. Changes from EDBP (D90±7) in disease severity from both clinician and patient/family perspective as quantified with the 'iscorEB' at M12±14 days and M24±14 days. Changes from OLP baseline (OLP D0) are obtained for the clinician and patient total scores only, separately. In addition, the change from baseline for the total iscorEB score will be obtained. If only one score is available (clinician or patient) due to the assessments not being performed, only the available score will be presented.

    If the assessment is not performed at D90±7 (due to patient discontinuation or if the patient is already ahead of day 90 of treatment) baseline values and all changes from baseline are set to "missing". If baseline values are available but one or more assessments are missing after baseline, the changes from baseline are obtained with the last observation carried forward. In addition, change from M12±14 days to M24±14 days will be also calculated as the value at M24±14 days – value at M12±14 days. Observed values and LOCF values will be summarized separately.

13. Changes from EDBP (D90±7) in patients' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with the 'EQ-5D' instrument at M12±14 days and M24±14 days. Changes from baseline are obtained only for the overall score. If the assessment is not performed at D90±7 (due to patient discontinuation or if the patient is already ahead of day 90 of treatment) baseline values and all changes from baseline are set to "missing". If baseline values are available but one or more assessments are missing after baseline, the changes from baseline are obtained with the last observation carried forward. Observed values and LOCF values will be summarized separately.

10. SAFETY

The population used for safety analyses is the SAF. Safety data will be analysed as follows:

- The analysis of the safety data for the DBP is performed after all data up to EDBP have been entered and cleaned, a database lock of these data has been performed and unblinding has been done. This analysis will be reported in the CSR (DBP).
- Interim OLP adverse event (all AE summary tables detailed in Section 10.1), local tolerability and laboratory data available at EDBP database lock will be analysed and reported in the CSR (DBP).
- Interim OLP adverse event (all AE summary tables detailed in Section 10.1), local tolerability and laboratory data available when all ongoing patients have had their Month 9 visits and Month 12 visits will be analysed and reported in line with regulatory requirements.
- The analysis of the complete safety data for the OLP is performed after database lock of the OLP and reported in the CSR (OLP).
- Adverse Events data will be presented in separate listings and tables for each study phase.
- For all other safety assessments (laboratory, vital signs, ECG, physical examination and local tolerability) data will be presented by visit, and in separate listings and tables for each study phase. If changes from baseline are applicable, tables will include change from DBP baseline (DBP D0) for DBP and change from OLP baseline (OLP DO) for OLP.

10.1. ADVERSE EVENTS

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs are coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology, and the severity of AEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.3.

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose:

- Results in death (death is an outcome, the condition leading to death is the SAE)
- Is life-threatening
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect

Important AEs may not be immediately life-threatening, result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent 1 of the other outcomes listed above. These AEs are also considered serious.

Adverse events occurring before the First Study Treatment are recorded in the Medical History/Current Medical Conditions section of the eCRF except those resulting from a protocol-mandated procedure, which should be reported in the AE/SAE section of the eCRF. AE/SAEs occurring during the DBP and the OLP or new AE/SAEs reported by patients up to 30 days after the last administration of study medication (Oleogel-S10 or vehicle) are recorded in the AE/SAE section of the eCRF. Worsening of wound status and increase in wound size compared to baseline as well as wound infections and wound re-opening are reported as AEs.

A severe AE is any AE recorded with a CTCAE grade 3 or higher. An AE causally related to the study medication is an AE recorded with one of the following causality categories: Certain, Probable, Possible. For a more conservative approach, any AE with missing causality or with either Conditional/Unclassified or Unclassifiable causality is also considered causally related to the study medication.

Treatment-Emergent Adverse Events (TEAEs) are those AEs that occur from the First Study Treatment to 4 weeks after the Last Study Treatment and do not necessarily have a causal relationship to the use of the study medication. TEAEs (simply referred to as adverse events in summary tables) are summarised.

Verbatim terms are mapped to PTs and SOCs using the current MedDRA version. For each SOCs and PT, frequency counts and percentages on a patient basis are calculated.

AEs presented by SOC in the overall column in decreasing order. Within each SOC, AEs are displayed by PT in decreasing order in the overall column.

The following adverse events summary tables are presented:

1. An overall summary of incidence of AEs
2. An overall summary of incidence of AEs by SOC and PT
3. A summary of AEs presented by PT in decreasing order in the Oleogel-S10 column
4. A summary of SAEs presented by PT in decreasing order in the Oleogel-S10 column
5. A summary of SAEs by SOC and PT
6. A summary of severe AEs by SOC and PT
7. A summary of AEs related to study medication by SOC and PT
8. A summary of SAEs related to study medication by SOC and PT
9. A summary of AEs leading to study discontinuation by SOC and PT
10. A summary of SAEs leading to study discontinuation by SOC and PT

11. A summary of AEs related to study medication and leading to study discontinuation by SOC and PT
12. A summary of SAEs related to study medication and leading to study discontinuation by SOC and PT
13. A summary of SAEs leading to death by SOC and PT
14. A summary of AEs due to wound complications (split by wound re-opening, wound worsening, increase in wound size, injury to the wound and wound infections as defined in Section 9.3) (identification of AEs related to wound complications will be done via medical review and the list provided to the programming team)
15. A summary of AEs based on the AE onset classified in the following duration of treatment exposure intervals (all intervals defined by the study visits):
    For DBP: D0-<1 month, 1 month-<2 months, 2 months-<=3 months;
    For OLP: OLP D0-<M3, M3-<M12, M12-<=M24.

    The number of patients included in each interval is cumulative in relation to the duration of exposure. The denominator for percentages in each interval is the number of patients with exposure (at least 1 day) cumulative in each prior exposure interval (i.e., current interval plus all previous intervals). Only those AEs with an onset in the interval are summarized.
16. A summary of AEs leading to drug discontinuation by SOC and PT

All AEs and SAEs are listed separately by AE start study day (study day will be derived as per Section 7.2.4 using the start date of the AE).
AEs are assigned to DBP if they have a start date between D0 and date of first study treatment date of the OLP (exclusive) and to the OLP if they have a start date on or after first study treatment date of the OLP.

10.2. LABORATORY EVALUATIONS

Laboratory safety assessments comprise haematology (full blood count with white blood cell differential); biochemistry panels (sodium [Na], potassium [K], calcium [Ca], chloride [Cl], phosphate [P], blood glucose [BG]) including renal (urea, creatinine) and hepatic function tests (serum total protein, albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], and alkaline phosphatase [AP]). Laboratory safety parameters are assessed at baseline (D0), at D90±7, at M12±14 days, and at M24±14 days. If haematology and biochemistry parameters have been determined within 4 weeks prior to enrolment, they may be used as baseline values.

Clinical laboratory values are listed and summarised descriptively including changes from baseline. Shift tables are used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.

Betulin levels are analysed in dried blood spots that are sent to the central laboratory (Nuvisan GmbH, Germany). Betulin data are also listed and summarised descriptively by type of blood sample (venous or capillary) including changes from baseline. For results that are below the limit of quantification: if the sample was taken before first drug

administration then the analysis value will be equal to zero; if the sample was taken after first drug administration then the analysis value will be equal to the lower limit of quantification divided by 2. Patients will be excluded from summary tables if type of blood sample is not available or if type of blood sample at baseline is not equal to the sample type for at least one subsequent visit. Patients will be included in type venous or capillary based on type at baseline, and only if type at baseline is equal to the sample type for at least one subsequent visit.

Urine pregnancy tests are conducted in women of childbearing potential/postmenarchal female adolescent patients at DBP baseline (D0) and EDBP (D90±7), and M3±14 days, M12±14 days, and M24±14 days of the OLP. Pregnancy data are listed only.

In the event of a suspected EB wound infection, the investigator should take a wound swab and the result is listed as recorded in the eCRF.

10.3. VITAL SIGNS

Vital signs (heart rate, respiratory rate, and body temperature) are recorded at baseline, at D90±7, and at M24±14 days at the OLP.

Absolute values and changes from baseline in vital signs are listed and summarised descriptively.

10.4. ELECTROCARDIOGRAM

An electrocardiogram (ECG) is performed at baseline, at D90±7 days (From Version 4 of Protocol), and at M24±14 days, where available. Note that due to the fragility of the skin for many EB patients, ECG electrodes cannot be used and hence it is anticipated that data may be missing for this assessment.

The ECG recordings are reviewed by the investigator and classified as “normal’ or ‘abnormal”. Abnormal ECGs must in addition be classified as “abnormal, clinically significant” or “abnormal, not clinically significant”. Abnormal, clinically significant findings occurring after first administration of study medication should be reported as an AE (unless already pre-existing at baseline with the same severity). Shift tables are used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.

All data are listed and summarised.

10.5. PHYSICAL EXAMINATION

The investigator does a complete physical examination of the patient at baseline, D90±7 days and M24±14 days and documents all clinically relevant findings including systemic manifestations of EB. Any new abnormal/worsening physical exam findings are collected as AEs. Physical Examination data are listed and summarised.

10.6. LOCAL TOLERABILITY

Local tolerability is judged by the investigator, monitored and documented continuously throughout the study. The results are listed and summarised descriptively.

Local tolerability issues will be identified and categorised into the following categories during Sponsor medical review: Pruritus, wound complication, administration site reactions, other. A spreadsheet categorising the local tolerability issues will be provided to the programming team. A frequency summary table of the local tolerability issues by the above categories will be presented for the SAF.

10.7. ANALYSIS OF DOUBLE-BLIND PHASE SAFETY ENDPOINTS

Safety endpoints are analysed using the SAF as described below:

1. Incidence, severity, and relatedness of AEs: Adverse events are summarised and provided as data listings separately by study phase. Verbatim terms are mapped to PTs and SOCs using the current MedDRA version. For each PT, the number of events as well as frequency counts and percentages are calculated. Separate analyses are conducted using severity, seriousness, and relationship to study medication.

2. Vital signs and clinical laboratory values are summarised descriptively. For clinical laboratory variables shift tables are used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.

3. Betulin data (patient fasting status and concentrations in ng/mL) are summarised descriptively by visit and by method of collection (venous or capillary).

4. Local tolerability as judged by the investigator is summarised descriptively as part of the “Study Drug Administration and Dressing Change” summary.

10.8. ANALYSIS OF OPEN-LABEL PHASE SAFETY ENDPOINTS

1. Incidence, severity, and relatedness of AEs: Adverse events are summarised in tables and provided as data listings as for the DBP. Tables will include the overall column for all patients combined treatment groups.

2. Vital signs and clinical laboratory values are summarised descriptively. For clinical laboratory variables shift tables are used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.

3. Betulin data (patient fasting status and concentrations in ng/mL) are summarised descriptively by visit and by method of collection (venous or capillary).

4. Local tolerability as judged by the investigator is summarised descriptively as part of the “Study Drug Administration and Dressing Change” summary.

10.9. SAFETY SUBGROUP ANALYSES

The following AE subgroup analyses will be performed on DBP data and interim OLP data at the EDBP, interim OLP data when ongoing patients have had their M9 visit, interim OLP data when ongoing patients have had their Month 12 visit and on the final OLP data at the EOLP. The betulin subgroup analyses will be performed on DBP data and OLP data at database lock for the DBP and OLP, respectively. All subgroup definitions will be based on the FAS.

10.9.1. Adverse Events

The AE tables for AEs (by SOC and PT), SAEs (by SOC and PT), AEs leading to study discontinuation (by SOC and PT) and SAEs leading to study discontinuation (by SOC and PT) will be repeated for the following subgroups:

- Age group [Young Children (<4 years), Children (4-11 years), Adolescents (12-17 years), Adults (>=18 years)]
- Gender [Female vs Male]
- Race [White, Black or African American, Asian, Other]
- Geographic Region [USA/Europe/South America/Rest of World]. The category "Rest of World" will include Russia, Israel, Georgia, Ukraine, Singapore, Hong Kong and Australia.
- Quantity of product (grams) used (categorized as 1st tertile, 2nd tertile, 3rd tertile based on the total amount of medication used in each study phase as derived using the formula in Section 8.5

10.9.2. Betulin Data

Betulin data will be analysed for the following subgroups:

- Age group [Young Children (<4 years), Children (4-11 years), Adolescents (12-17 years), Adults (>=18 years)]
- Gender [Female vs Male]
- BMI at DBP D0:

  For paediatric patients (0 to <18 years old):

  - If patient is under 5 years old, BMI will be categorized as suggested by WHO for child growth standards (https://www.who.int/childgrowth/standards/bmi_for_age/en/). For patients under one year of age the age in months will be utilized for categorization, and for patients over one year of age the age in full years will be utilized.
  - If patient is between 5 to <18 years old, BMI will be categorized as suggested by WHO for growth reference standards

(https://www.who.int/growthref/who2007_bmi_for_age/en/). The age in full years will be utilized for categorization.

Using the two standards above for expected BMI per-age for each patient-age will be categorized as:

- Underweight: below the 5th percentile
- Normal weight: between the 5th percentile to 85th percentile
- Overweight: between the 85th to 94th percentiles
- Obese: at or above the 95th percentile

For adults (>=18 years old):

BMI will be categorized as suggested by WHO based on nutritional status (http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi) as:

- Underweight: < 18.5 kg/m^2
- Normal weight: 18.5 kg/m^2– 24.9 kg/m^2
- Overweight: 25 kg/m^2– 29.9 kg/m^2
- Obese: ≥30 kg/m^2

- Baseline at DBP D0 Total wound burden [mild: EBDASI Total Score 0-42, moderate: 43-106, severe: >106]
- Baseline at DBP D0 Total BSAP (<10%, 10-25%, >25%)
- Quantity of product (grams) used (categorized as 1st tertile, 2nd tertile, 3rd tertile based on the total amount of medication used in each study phase as derived using the formula in Section 8.5
- Baseline at DBP D0 Total wound area, derived as follows:

  total BSA * total BSAP/100

  where total BSA (m^2) = [√(height(cm)*weight(kg)/3600)], and total BSAP (%) is the sum of total BSAP (%) per region as recorded in the eCRF. Total wound area will be categorized as <0.1m^2, 0.1-0.3m^2, >0.3m^2.

If deemed necessary for a meaningful analysis, categories might be further combined together to reduce the number of subgroups.

11. IDMC AND INTERIM ANALYSES

An IDMC was established to review and evaluate efficacy and safety data during the DBP of the study. The board consists of independent experts who are not involved in the study.

Interim IDMC safety reviews are conducted to ensure safety for participants and to advise regarding continuation, modification, or discontinuation of individual patients and/or of the futility of the study. Blinded safety reviews could occur any time should questions of patient safety arise during the DBP and to review Serious Adverse Events (SAEs) that require expedited reporting to a regulatory agency.

An unblinded interim IDMC review on PK data was also conducted of 6 children between 4 and 11 years following 90 days of DBP, plus at least the same number of older children and adults. Following this review, the IDMC recommended to expand the inclusion of children with Epidermolysis Bullosa to all ages i.e. ≥21 days and <4 years.

An unblinded interim analysis for sample size re-estimation took place when approximately 50% of patients completed D45±7. The IA included an unblinded sample size re-estimation using the CHW approach and a computation of the conditional power to check for futility (Cui, Hung et al. 1999). In addition to the analysis of the primary efficacy endpoint, the IA also included results of some selected secondary efficacy endpoints (descriptive summaries only) to allow the IDMC the flexibility to recommend study continuation in the event that the conditional power is <80% with the maximum sample size allowed.

Based on the results of the sample size re-estimation, the IDMC recommended to increase the sample size by 48 patients (24 per arm) to a total of 230 evaluable patients. A total of 250 patients are planned to be enrolled into the study and treated to account for drop-out patients.

The CHW weighted test-statistics for consideration of sample size re-estimation did not require an adjustment of the significance level for the sample size increase after the IA. Discussion of various potential scenarios and further details and assumptions at the IA influencing the re-estimation of the sample size and the analysis of the primary efficacy endpoint are available in the separate document “Sample Size Report for Re-estimation”.

An interim OLP safety analysis was performed once all ongoing patients had completed their Month 9 OLP visits. The analysis outputs were based on the SAF.

An interim OLP safety and efficacy analysis is to be performed once all ongoing patients have completed their Month 12 OLP visits.

The interim OLP safety and efficacy analysis will contain all OLP efficacy (see section 9.6) and safety outputs (see section 10.8) as well as other relevant outputs which have updated data and additional efficacy outputs specified below.

The interim OLP safety analysis outputs will be based on the SAF.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

1. An important update from Protocol Version 3.0 (the first protocol version used to enrol a patient) to Protocol Version 4.0 was the exclusion of the EB Simplex (EBS) patients from enrolment in the study. In case EBS patients were recruited before Protocol Version 4.0 was implemented, these patients are included in all data listings, summary tables and figures, and are included in the corresponding analysis population following the criteria presented in Section 6. For stratified analyses, recruited EBS patients are included in the strata defined by the DEB subtype, and sensitivity analyses for the primary efficacy endpoint and key secondary endpoint may be performed.

2. In case patients from a randomization stratum were incorrectly stratified, a comment to explain this is recorded in the eCRF or the protocol deviation log, and the patient is included in the correct stratum for all analyses described in this SAP.

3. Efficacy data will be analysed based on the actual visit date rather than the nominal visit day. Each value will be re-assigned to a visit window based on the actual study day and one value will be selected for each time-point for the efficacy analyses, as explained in Section 7.4.

4. Based on the data collected in the database, it is not possible to adjust treatment compliance for the variation in medication applications due to changes in wounds and differences in frequencies of dressing changes.

5. Subgroup analyses have been added for the Primary Efficacy Endpoint and the Key Secondary Efficacy Endpoints of DBP (see Section 9.4.3 for more details).

6. There are several changes regarding the efficacy endpoints for the OLP (see Section 9.6 for more details):

- Analyses for proportion of patients with complete closure and time to complete closure have been eliminated

- Analyses for comparisons of incidence rates of wound infection between DBP versus OLP have been added.

- Analyses for comparisons of changes from baseline between DBP versus OLP (using paired t-tests) have been added.

7. Subgroup analyses for AEs and Betulin data have been added (see Section 10.9 for more details)

8. As discussed in Section 2.2, the Sponsor decided to cease enrolment after 223 patients had been enrolled into the study and proceed to database lock of the double-blind phase. Thus the study includes 223 patients eligible for the primary efficacy analysis (223/230=97% of planned number of evaluable patients).

9. An additional Interim OLP Safety analysis (As discussed in Section 2.2 and Section 11) is performed for the FDA 90-Day Safety Update Report.

10. An additional Interim OLP Efficacy and Safety analysis (As discussed in Section 2.2 and Section 11) is performed due to EMA request.

11. The analysis performed for efficacy at Month 12 and Month 24 was updated to use a new visit window. Previously a year was considered to have 360 days (that is 30 days per month), however it was noted that when capturing the data at the investigator sites, the conventional year length of 365 days was generally used. Thus, the windowing was updated to 365 days ±14 days for a M12 and 730 days ±14 days for a M24.

12. Post-hoc outputs relating to EBDASI and BSAP were created without visit windowing for OLP visits (i.e. using the exact day a patient had a visit and not shifting them into the predefined visit windows to which they best fit) in order to accurately reflect real world data.

13. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses are generated using SAS® for Windows, Release 9.3 or later (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output adheres to the following specifications.

13.1. GENERAL CONSIDERATIONS

- A separate SAS program is created for each output.
- Each output is stored in a separate file.
- Output files are delivered in Word format / pdf format.
- Numbering of TFLs follows ICH E3 guidance

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs are produced in landscape format (A4), if suitable for an FDA submission and unless otherwise specified.
- All TLFs are produced using the Courier New font, size 8
- The data displays for all TLFs have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures are in Courier New font, size 8.
- Legends are used for all figures with more than 1 variable, group, or item displayed.
- TLFs are in black and white (no colour), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, are not used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters are used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, are not used. Hexadecimal-derived characters are used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) are employed on a case-by-case basis.
- Mixed case are used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

  Amryt Protocol BEB-13 (Syneos Health study number 1008121)

Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centred. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins separates the display titles from the column headers. There is 1 blank line between the last title and the solid line.

Table x.y.z

First Line of Title

Second Line of Title if Needed

ITT Analysis Set

13.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes are presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.
- The order of treatments in the tables and listings are Active comparators first, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units are included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages are not presented and so any counts of 0 are presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 is presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)) except for zero counts that will be presented as “0” with no decimals. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation is the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOCs with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOCs, medical history (by preferred term), drugs (by ATC1 and ATC4 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed.
- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, describe in a footnote or programming note if the patient should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

13.2.5.3. Listing Conventions

- Listings are sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on patient listings as blank.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time is only reported if it was measured as part of the study.

  Units are included where available

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits are displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values are displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins separates the body of the data display from the footnotes.
- All footnotes are left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Patient specific footnotes should be avoided, where possible.
- Footnotes are used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section is a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

14. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. REFERENCE LIST

15.1. SOURCE DOCUMENTS

Clinical Study Protocol "Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa", Version 3.0 dated 16 February 2017.

Clinical Study Protocol "Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa", Version 4.0 dated 20 April 2018.

Clinical Study Protocol "Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa", Version 5.0 dated 01 October 2018.

Clinical Study Protocol "Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa", Version 6.0 dated 18 April 2019.

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"Sample Size Report for Re-estimation", Version 2.0 dated 07-Dec-2018.

15.2. LITERATURE

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Bruckner-Tuderman, L. and C. Has (2012). "Molecular heterogeneity of blistering disorders: the paradigm of epidermolysis bullosa." J Invest Dermatol **132**(E1): E2-5.

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16. INDEX OF TABLES, LISTINGS AND FIGURES

Below is the index of Tables and Figures and the index of Listings. Possible deviations in the index are not considered deviations from the SAP.

In the indexes below "DBP" denotes outputs required for the EDBP analysis and "OLP" denotes outputs required for the EOLP analysis.

16.1. INDEX OF TABLES AND FIGURES

Table Number	Table Title	DBP	OLP
Table 14.1.1.1	Summary of Patient Disposition (All Enrolled Patients)***	Yes	Yes
Table 14.1.1.2	Summary of Patient Visits (Safety Analysis Set)	Yes	Yes
Table 14.1.2.1	Summary of Major Protocol Deviations (Safety Analysis Set)	Yes	Yes
Table 14.1.2.2	Summary of Minor Protocol Deviations (Safety Analysis Set)	Yes	Yes
Table 14.1.2.3	Analysis Sets and Reasons for Exclusion from Analysis Sets (All Randomized Patients)	Yes	No
Table 14.1.3.1.1	Demographics and Baseline Characteristics (Safety Analysis Set)***	Yes	Yes
Table 14.1.3.1.2	Baseline Characteristics for Subgroup Variables (Safety Analysis Set)	Yes	Yes
Table 14.1.3.2.1	Summary of EB Subtype and Method of Diagnosis (Safety Analysis Set)***	Yes	No
Table 14.1.3.2.2.1	Summary of Wound Selection – Target Wounds (Safety Analysis Set)***	Yes	No
Table 14.1.3.2.2.2	Summary of Wound Selection – Additional Wounds (Safety Analysis Set)	Yes	No
Table 14.1.3.3	Summary of Medical History (Safety Analysis Set)	Yes	No
Table 14.1.4.1	Summary of Prior Medications (Safety Analysis Set)	Yes	No
Table 14.1.4.2	Summary of Concomitant Medications (Safety Analysis Set)	Yes	Yes
Table 14.1.4.3	Summary of Concomitant Medications throughout the Study (Safety Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Table 14.1.4.4	Summary of OLP Concomitant Medications – OLP Data (Safety Analysis Set)	No	Yes
Table 14.1.5.1	Summary of Study Drug Administration and Dressing Change by Visit (Safety Analysis Set)	Yes	Yes
Table 14.1.5.2	Summary of Treatment Compliance (Safety Analysis Set)	Yes	Yes
Table 14.1.5.3	Summary of Returned Study Medication by Visit (Safety Analysis Set)	Yes	Yes
Table 14.2.1.1.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test adjusted with CHW (Full Analysis Set)***	Yes	No
Table 14.2.1.1.2	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test (Completer Analysis Set)	Yes	No
Table 14.2.1.1.3	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test (Per Protocol Set)	Yes	No
Table 14.2.1.2.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment Confirmed by a Second Observation after 7 Days -- stratified CMH test (Full Analysis Set)	Yes	No
Table 14.2.1.3.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Fisher's Exact Test (Full Analysis Set)	Yes	No
Table 14.2.1.3.2	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Fisher's Exact Test (Completer Analysis Set)	Yes	No
Table 14.2.1.3.3	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Fisher's Exact Test (Per Protocol Set)	Yes	No
Table 14.2.1.3.4	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment Confirmed by a Second Observation after 7±2 Days -- Non-stratified Fisher's Exact Test (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Post-Hoc Table 14.2.1.3.5	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Fisher's Exact Test – RDEB Patients by Age Group (Full Analysis Set)	Yes	No
Post-Hoc Table 14.2.1.3.6	Proportion of Patients with First Complete Closure of EB Target Wound within D90±7, Clinical Assessment -- Non-stratified Fisher's Exact Test – RDEB Patients by Age Group (Full Analysis Set)	Yes	No
Table 14.2.1.4.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Chi-Square Test (Full Analysis Set)	Yes	No
Table 14.2.1.4.2	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Chi-Square Test (Completer Analysis Set)	Yes	No
Table 14.2.1.4.3	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Chi-Square Test (Per Protocol Set)	Yes	No
Table 14.2.1.4.4	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment Confirmed by a Second Observation after 7±2 Days -- Non-stratified Chi-Square Test (Full Analysis Set)	Yes	No
Table 14.2.1.5.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Logistic Regression Model (Full Analysis Set)	Yes	No
Table 14.2.1.6.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test with “Worst Case” Imputation for Missing Values (Full Analysis Set)	Yes	No
Table 14.2.1.7.1	Proportion of Patients with Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.1.8.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test by Wound Contact Layer/Dressing Type (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.2.1.9.1	Proportion of Patients with First Complete Closure of EB Target Wound and no Re-opening prior to or at D45±7, Clinical Assessment -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.1.10.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test with "Worst Case" Imputation for Missing Values due to COVID-19 (Full Analysis Set)***	Yes	No
Table 14.2.1.11.1	Time to First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified Log-rank test (Full Analysis Set)	Yes	No
Figure 14.2.1.11.2	Kaplan-Meier Curve for Time to First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Non-stratified (Full Analysis Set)	Yes	No
Table 14.2.1.12.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by EB Subtype - (Full Analysis Set)	Yes	No
Table 14.2.1.12.2	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Size of Target Wound - (Full Analysis Set)	Yes	No
Table 14.2.1.12.3	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Age Group - (Full Analysis Set)	Yes	No
Table 14.2.1.12.4	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Gender - (Full Analysis Set)	Yes	No
Table 14.2.1.12.5	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Race - (Full Analysis Set)	Yes	No
Table 14.2.1.12.6	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Contact Layer/Dressing - (Full Analysis Set)	Yes	No
Table 14.2.1.12.7	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Baseline Nutritional Status - (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.2.1.12.8	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Baseline Anaemia - (Full Analysis Set)	Yes	No
Table 14.2.1.12.9	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – by Baseline Renal Function - (Full Analysis Set)	Yes	No
Figure 14.2.1.12.10	Forest Plot of the proportion of patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment (Full Analysis Set)-- Stratified CMH Test – Summary of Subgroup Analyses - (Full Analysis Set)***	Yes	No
Table 14.2.1.13.1	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test – with Multiple Imputation using the Tipping Point Approach (Full Analysis Set)	Yes	No
Table 14.2.2.1.1.1	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank test (Full Analysis Set)***	Yes	No
Table 14.2.2.1.1.2	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test (Completer Analysis Set)	Yes	No
Table 14.2.2.1.1.3	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test (Per Protocol Set)	Yes	No
Figure 14.2.2.1.1.4	Kaplan-Meier Curve for Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified (Full Analysis Set)***	Yes	No
Figure 14.2.2.1.1.5	Kaplan-Meier Curve for Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified (Completer Analysis Set)	Yes	No
Figure 14.2.2.1.1.6	Kaplan-Meier Curve for Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified (Per Protocol Set)	Yes	No
Table 14.2.2.1.2.1	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment – Log-rank Test Stratified by EB Subtypes (Full Analysis Set))	Yes	No

Table Number	Table Title	DBP	OLP
Figure 14.2.2.1.2.2	Kaplan-Meier Curve for Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Stratified by EB Subtypes (Full Analysis Set)	Yes	No
Table 14.2.2.1.2.3	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Cox regression model (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.1	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by EB Subtype (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.2	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Size of Target Wound - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.3	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Age Group - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.4	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Gender - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.5	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Race - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.6	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Contact Layer/Dressing - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.7	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Baseline Nutritional Status - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.8	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Baseline Anaemia - (Full Analysis Set)	Yes	No
Table 14.2.2.1.3.9	Time to First Complete Closure of EB Target Wound until EDBP (D90±7), Clinical Assessment -- Non-stratified Log-rank Test - by Baseline Renal Function - (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.2.2.2.1	Proportion of Patients with First Complete Closure of EB Target wound within D90±7, Clinical Assessment -- Stratified CMH Test (Full Analysis Set)***	Yes	No
Table 14.2.2.2.2	Summary of Closure of Wounds by Visit - Clinical Assessments (Full Analysis Set)	Yes	No
Table 14.2.2.2.3	Summary of Closure of Wounds by Visit - Patient Assessments (Full Analysis Set)	Yes	No
Post-Hoc Table 14.2.2.2.4	Proportion of Patients with First Complete Closure of EB Target Wound within D90±7, Clinical Assessment -- Stratified CMH Test – by EB Subtype (Full Analysis Set)	Yes	No
Post-Hoc Table 14.2.2.2.5	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment -- Stratified CMH Test - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	No
Post-Hoc Table 14.2.2.2.6	Proportion of Patients with First Complete Closure of EB Target Wound within D90±7, Clinical Assessment -- Stratified CMH Test - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	No
Table 14.2.2.2.7	Summary of Closure of Wounds by Visit – OLP Data - Clinical Assessments (Full Analysis Set)	No	Yes
Table 14.2.2.3.1	Incidence of Target Wound Infection between Baseline and D90±7 – Stratified CMH Test (Full Analysis Set)***	Yes	No
Table 14.2.2.3.2	Incidence of Target Wound Infection between Baseline and D90±7 -- Stratified CMH Test – for Subgroup of Patients used Medication in all wounds (Full Analysis Set)	Yes	No
Table 14.2.2.3.3	Incidence of Target Wound Infection (Bacteriologically Confirmed) between Baseline and D90±7 -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.2.3.4	Incidence of Target Wound Infection (Bacteriologically Confirmed) between Baseline and D90±7 -- Stratified CMH Test – for Subgroup of Patients who used Medication in all wounds (Full Analysis Set)	Yes	No
Table 14.2.2.3.5	Summary of Incidence of Wound Infection between Baseline and D90±7 (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.2.2.3.6	Incidence of Target Wound Infection Comparison between DBP Baseline and D90±7 versus OLP Baseline and M3±14 for Patients Randomized to Control Gel who have Unhealed Target Wounds at EDBP -- McNemar Test (Full Analysis Set)	No	Yes
Post-Hoc Table 14.2.2.3.7	Incidence of Target Wound Infection between Baseline and D90±7 - Stratified CMH Test - [redacted] considered as a patient with other wound infection instead of target wound infection - (Full Analysis Set)	Yes	No
Post-Hoc Table 14.2.2.3.8	Summary of Incidence of Wound Infection between Baseline and D90±7 - [redacted] considered as a patient with other wound infection instead of target wound infection - (Full Analysis Set)	Yes	No
Table 14.2.2.4.1	Maximum Severity of Target Wound Infection between Baseline and D90±7 --Wilcoxon Rank Sum Test Stratified (Full Analysis Set)***	Yes	No
Table 14.2.2.4.2	Summary of Maximum Severity of Wound Infection between Baseline and D90±7 (Full Analysis Set)	Yes	No
Table 14.2.2.4.3	Maximum Severity of Target Wound Infection between Baseline (OLP D0) and M24±14 -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	No	Yes
Table 14.2.2.4.4	Summary of Maximum Severity of Wound Infection between Baseline (OLP D0) and M24±14 (Full Analysis Set)	No	Yes
Table 14.2.2.5.1	Change from Baseline in Total Body Wound Burden based on EBDASI by Visit -- ANCOVA Model for Anatomic Locations and Total Activity Score (Full Analysis Set)***	Yes	Yes
Table 14.2.2.5.2	Total Body Wound Burden based on EBDASI by Visit -- Summary Statistics of Anatomic Locations and Total Activity Score (Full Analysis Set)	Yes	Yes
Table 14.2.2.5.3	Change from Baseline Comparison in Total Body Wound Burden based on EBDASI between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.5.4	Change from Baseline Comparison in Total Body Wound Burden based on EBDASI between OLP Baseline and M12±14 versus OLP Baseline and M24±14 - Paired t-test (Full Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Post-Hoc Table 14.2.2.5.4.1	Change from Baseline in Total Body Wound Burden based on EBDASI by Visit -- ANCOVA Model for Anatomic Locations and Total Activity Score – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.5.5	Total Body Wound Burden based on EBDASI by Visit -- Summary Statistics of Total Activity Score Anatomic Locations – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.5.6	Change from Baseline in Total Body Wound Burden based on EBDASI by Visit -- ANCOVA Model for Anatomic Locations and Total Activity Score - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.5.7	Total Body Wound Burden based on EBDASI by Visit -- Summary Statistics of Total Activity Score Anatomic Locations - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Table 14.2.2.5.8	Total Body Wound Burden based on EBDASI by Visit – OLP Data – Summary Statistics of Total Activity Score Anatomic Locations (Full Analysis Set)	No	Yes
Table 14.2.2.6.1	Change from Baseline in Itching before Wound Dressing Changes using Itch Man Scale by Visit in Patients >= 4 Years and up to 13 Years of Age -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)***	Yes	Yes
Table 14.2.2.6.2	Change from Baseline in Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Wilcoxon Rank Sum Test Stratified (Full Analysis Set)***	Yes	Yes
Table 14.2.2.6.3	Change from Baseline in Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Wilcoxon Rank Sum Test Stratified – Supportive Analysis (Full Analysis Set)	Yes	Yes
Table 14.2.2.6.4	Itching using Itch Man Scale by Visit in Patients >= 4 Years and up to 13 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.6.5	Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.6.6	Change from Baseline Comparison in Itching using Itch Man Scale in Patients >=4 Years and up to 13 Years of Age between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Table 14.2.2.6.7	Change from Baseline Comparison in Itching using Leuven Itch Scale in Patients >=14 Years of Age between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Post-Hoc Table 14.2.2.6.8	Change from Baseline in Itching before Wound Dressing Changes using Itch Man Scale by Visit in Patients >= 4 Years and up to 13 Years of Age -- Wilcoxon Rank Sum Test Stratified – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.9	Itching using Itch Man Scale by Visit in Patients >= 4 Years and up to 13 Years of Age – Summary Statistics – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.10	Change from Baseline in Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Wilcoxon Rank Sum Test Stratified – Supportive Analysis with Imputation at Baseline (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.11	Change from Baseline in Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Wilcoxon Rank Sum Test Stratified – Supportive Analysis – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.12	Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – Summary Statistics – Supportive Analysis - by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.13	Change from Baseline in Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age - Wilcoxon Rank Sum Test Stratified - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.6.14	Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age - Summary Statistics - Supportive Analysis - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Table 14.2.2.6.15	Itching using Itch Man Scale by Visit in Patients >= 4 Years and up to 13 Years of Age – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.6.16	Itching using Leuven Itch Scale by Visit in Patients >= 14 Years of Age – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Table 14.2.2.7.1	Proportion of Patients with First Complete Closure of EB Target Wound by Visit, Clinical Assessment -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.2.7.2	Proportion of Patients with First Complete Closure of EB Target Wound by Visit, Patient Assessment -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.2.7.3	Proportion of Patients with First Complete Closure of EB Target Wound by Visit, based on Blinded Evaluation of Photographs -- Stratified CMH Test (Full Analysis Set)	Yes	No
Table 14.2.2.7.4	Proportion of Patients with First Complete Closure of at least one EB Non-target Wound by Visit, Clinical Assessment -- Stratified CMH Test (Full Analysis Set) - Subset of Patients that have an Additional Wound Identified	Yes	No
Table 14.2.2.8.1	Percentage Change from Baseline in Size of EB Target Wound by Visit, Photographic Assessment -- ANCOVA Model (Full Analysis Set)	Yes	No
Table 14.2.2.8.2	Percentage Change from Baseline in Size of EB Target Wound by Visit, Photographic Assessment -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	No
Table 14.2.2.8.3	Size of EB Target Wound by Visit, Photographic Assessment – Summary Statistics (Full Analysis Set)	Yes	No
Figure 14.2.2.8.4	Boxplot of the Percentage Change from Baseline in Size of EB Target Wound by Visit, Photographic Assessment (Full Analysis Set)	Yes	No
Table 14.2.2.8.5	Percentage Change from Baseline in Size of EB Target Wound by Visit, Photographic Assessment – OLP Data - ANCOVA Model (Full Analysis Set)	No	Yes
Table 14.2.2.8.6	Percentage Change from Baseline in Size of EB Target Wound by Visit, Photographic Assessment – OLP Data- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	No	Yes
Table 14.2.2.8.7	Size of EB Target Wound by Visit, Photographic Assessment – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.9.1	Average Percentage Change from Baseline in Size of all EB Non-target (Additional) Wounds by Visit, Photographic Assessment -- ANCOVA Model (Full Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.2.2.9.2	Average Percentage Change from Baseline in Size of all EB Non-target (Additional) Wounds by Visit, Photographic Assessment -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	No
Table 14.2.2.9.3	Average Size of all EB Non-target (Additional) Wounds by Visit, Photographic Assessment – Summary Statistics (Full Analysis Set)	Yes	No
Figure 14.2.2.9.4	Boxplot of the Average Percentage Change from Baseline in Size of all EB Non-target (Additional) Wounds by Visit, Photographic Assessment (Full Analysis Set)	Yes	No
Table 14.2.2.10.1	Change from Baseline in Total BSAP of TBSA Affected by EB Partial Thickness Wounds based on "Lund and Browder" Chart by Visit -- ANCOVA Model (Full Analysis Set)	Yes	Yes
Table 14.2.2.10.2	BSAP of TBSA affected by EB Partial Thickness Wounds based on “Lund and Browder” Chart for each Anatomic Region and Total BSAP by Visit – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.10.3	Change from Baseline Comparison in BSAP of TBSA Affected by EB Partial Thickness Wounds between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.10.4	Change from Baseline Comparison in BSAP of TBSA Affected by EB Partial Thickness Wounds between OLP Baseline and M12±14 versus OLP Baseline and M24±14 - Paired t-test (Full Analysis Set)	No	Yes
Post-Hoc Table 14.2.2.10.4.1	Change from Baseline in Total BSAP of TBSA Affected by EB Partial Thickness Wounds based on "Lund and Browder" Chart by Visit -- ANCOVA Model – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.10.5	BSAP of TBSA affected by EB Partial Thickness Wounds based on “Lund and Browder” Chart for each Anatomic Region and Total BSAP by Visit – Summary Statistics – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.10.6	Change from Baseline in Total BSAP of TBSA Affected by EB Partial Thickness Wounds based on "Lund and Browder" Chart by Visit -- ANCOVA Model - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Post-Hoc Table 14.2.2.10.7	BSAP of TBSA affected by EB Partial Thickness Wounds based on "Lund and Browder" Chart for each Anatomic Region and Total BSAP by Visit - Summary Statistics - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Table 14.2.2.10.8	BSAP of TBSA affected by EB Partial Thickness Wounds based on “Lund and Browder” Chart for each Anatomic Region and Total BSAP by Visit – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.11.1	Change from Baseline in Background Pain Before Wound Dressing Changes by Visit in Patients < 4 Years of Age using the FLACC Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.2	Background Pain Before Wound Dressing Changes using the FLACC Pain Rating Scale by Visit in Patients < 4 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.3	Change from Baseline in Background Pain Before Wound Dressing Changes by Visit in Patients >= 4 Years of Age using the Wong-Baker Faces Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.4	Background Pain Before Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.5	Change from Background Pain Before Wound Dressing Changes by Visit using Combination of FLACC and Wong-Baker Faces Pain Rating Scales -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.6	Background Pain Before Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scales by Visit – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.11.7	Change from Baseline Comparison in Background Pain Before Wound Dressing Changes using the FLACC Pain Rating Scale between DBP Baseline and D90±7 versus OLP Baseline and M3±14 in Patients < 4 Years of Age - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.11.8	Change from Baseline Comparison in Background Pain Before Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale between DBP Baseline and D90±7 versus OLP	No	Yes

Table Number	Table Title	DBP	OLP
	Baseline and M3±14 in Patients >= 4 Years of Age - Paired t-test (Full Analysis Set)		
Table 14.2.2.11.9	Change from Baseline Comparison in Background Pain Before Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scale between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.11.10	Background Pain Before Wound Dressing Changes using the FLACC Pain Rating Scale by Visit in Patients < 4 Years of Age – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.11.11	Background Pain Before Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.11.12	Background Pain Before Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scales by Visit – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.12.1	Change from Baseline in Procedural Pain After Wound Dressing Changes by Visit in Patients < 4 Years of Age using the FLACC Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.2	Procedural Pain After Wound Dressing Changes using the FLACC Pain Rating Scale by Visit in Patients < 4 Years of Age - Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.3	Change from Baseline in Procedural Pain After Wound Dressing Changes by Visit in Patients >= 4 Years of Age using the Wong-Baker Faces Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.4	Procedural Pain After Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age - Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.5	Change from Procedural Pain After Wound Dressing Changes by Visit using Combination of FLACC and Wong-Baker Faces Pain Rating Scales -- Wilcoxon Rank Sum Test Stratified (Full Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.2.2.12.6	Procedural Pain After Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scales by Visit – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.7	Change from Baseline Comparison in Procedural Pain After Wound Dressing Changes using the FLACC Pain Rating Scale between DBP Baseline and D90±7 versus OLP Baseline and M3±14 in Patients < 4 Years of Age - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.12.8	Change from Baseline Comparison in Procedural Pain After Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale between DBP Baseline and D90±7 versus OLP Baseline and M3±14 in Patients >= 4 Years of Age - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.12.9	Change from Baseline Comparison in Procedural Pain After Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scale between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Post-Hoc Table 14.2.2.12.10	Change from Baseline in Procedural Pain After Wound Dressing Changes by Visit in Patients >= 4 Years of Age using the Wong-Baker Faces Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.12.11	Change from Baseline in Procedural Pain After Wound Dressing Changes by Visit in Patients >= 4 Years of Age using the Wong-Baker Faces Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified – by Age Group (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.12.12	Procedural Pain After Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age – Summary Statistics – by EB Subtype (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.12.13	Procedural Pain After Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age – Summary Statistics – by Age Group (Full Analysis Set)	Yes	Yes
Post-Hoc Table 14.2.2.12.14	Change from Baseline in Procedural Pain After Wound Dressing Changes by Visit in Patients >= 4 Years of Age using the Wong-Baker Faces Pain Rating Scale -- Wilcoxon Rank Sum Test Stratified - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Post-Hoc Table 14.2.2.12.15	Procedural Pain After Wound Dressing Changes using the Wong-Baker Faces Pain Rating Scale by Visit in Patients >= 4 Years of Age - Summary Statistics - RDEB Generalised Severe Patients - (Full Analysis Set)	Yes	Yes
Table 14.2.2.12.16	Procedural Pain After Wound Dressing Changes using the FLACC Pain Rating Scale by Visit in Patients < 4 Years of Age – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.12.17	Procedural Pain After Wound Dressing Changes using Combination of FLACC and Wong-Baker Faces Pain Rating Scales by Visit – OLP Data - Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.13.1	Change from Baseline in the Impact of Wounds on Sleep using W-QoL Scale by Visit in Patients >= 14 years of Age - ANCOVA Model (Full Analysis Set)	Yes	Yes
Table 14.2.2.13.2	Impact of Wounds on Sleep using W-QoL Scale by Visit in Patients >= 14 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.13.3	Change from Baseline Comparison in the Impact of Wounds on Sleep using W-QoL between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.14.1	Number of Days Missed from School or from Work – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.14.2	Change from Baseline Comparison in Number of Days Missed from School or from Work between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes
Table 14.2.2.15.1	Treatment Satisfaction using the TSQM Overall Score by Visit in Patients >= 14 Years of Age -- ANCOVA Model (Full Analysis Set)	Yes	Yes
Table 14.2.2.15.2	Treatment Satisfaction Questionnaire for Medication (TSQM) by Visit in Patients >= 14 Years of Age – Summary Statistics (Full Analysis Set)	Yes	Yes
Table 14.2.2.15.3	Change from Baseline Comparison in Treatment Satisfaction using the TSQM Overall Score between DBP Baseline and D90±7 versus OLP Baseline and M3±14 - Paired t-test (Full Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Table 14.2.2.16.1	Disease Severity using the iScorEB Score by Visit – Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.16.2	Disease Severity using the iScorEB Score by Visit – Summary Statistics using LOCF (Full Analysis Set)	No	Yes
Table 14.2.2.16.3	Disease Severity using the iScorEB Score by Visit– Changes from M12±14 to M24±14 days (Full Analysis Set)	No	Yes
Table 14.2.2.16.4	Disease Severity using the iScorEB Score by Visit – Changes from M12±14 to M24±14 days using LOCF (Full Analysis Set)	No	Yes
Table 14.2.2.17.1	Health-related Quality of Life by Visit using the EQ-5D Scale– Summary Statistics (Full Analysis Set)	No	Yes
Table 14.2.2.17.2	Health-related Quality of Life by Visit using the EQ-5D Scale – Summary Statistics using LOCF (Full Analysis Set)	No	Yes
Table 14.2.2.17.3	Health-related Quality of Life by Visit using the EQ-5D scale VAS– Summary statistics (Full Analysis Set)	No	Yes
Table 14.2.2.17.4	Health-related Quality of Life by Visit using the EQ-5D scale VAS – Summary statistics using LOCF (Full Analysis Set)	No	Yes
Table 14.3.1.1.1	Summary of Treatment-Emergent Adverse Events – Overall Summary (Safety Analysis Set)***	Yes	Yes
Table 14.3.1.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)***	Yes	Yes
Table 14.3.1.1.3	Summary of Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.4	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)***	Yes	Yes
Table 14.3.1.1.5	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.6	Summary of Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.7	Summary of Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)***	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.1.1.8	Summary of Serious Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.9	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term (Safety Analysis Set)***	Yes	Yes
Table 14.3.1.1.10	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.11	Summary of Related Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.12	Summary of Serious Related Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.13	Summary of Serious Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.14	Summary of Treatment-Emergent Adverse Events Due to Wound Complications (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.15	Summary of Treatment-Emergent Adverse Events based on the Adverse Event Onset and classified by the Duration of Treatment Exposure Intervals by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.1.16	Summary of Treatment-Emergent Adverse Events Leading to Drug Withdrawal by System Organ Class and Preferred Term (Safety Analysis Set)	Yes	Yes
Table 14.3.1.2.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Age Group (Safety Analysis Set)	Yes	Yes
Table 14.3.1.2.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Gender (Safety Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.1.2.3	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Race (Safety Analysis Set)	Yes	Yes
Table 14.3.1.2.4	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Geographic Region (Safety Analysis Set)	Yes	Yes
Table 14.3.1.2.5	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Quantity of Product Used (Safety Analysis Set)	Yes	Yes
Table 14.3.1.3.1	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Age Group (Safety Analysis Set)	Yes	Yes
Table 14.3.1.3.2	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Gender (Safety Analysis Set)	Yes	Yes
Table 14.3.1.3.3	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Race (Safety Analysis Set)	Yes	Yes
Table 14.3.1.3.4	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Geographic Region (Safety Analysis Set)	Yes	Yes
Table 14.3.1.3.5	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- by Quantity of Product Used (Safety Analysis Set)	Yes	Yes
Table 14.3.1.4.1	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Age Group (Safety Analysis Set)	Yes	Yes
Table 14.3.1.4.2	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Gender (Safety Analysis Set)	Yes	Yes
Table 14.3.1.4.3	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Race (Safety Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.1.4.4	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Geographic Region (Safety Analysis Set)	Yes	Yes
Table 14.3.1.4.5	Summary of Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Quantity of Product Used (Safety Analysis Set)	Yes	Yes
Table 14.3.1.5.1	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Age Group (Safety Analysis Set)	Yes	Yes
Table 14.3.1.5.2	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Gender (Safety Analysis Set)	Yes	Yes
Table 14.3.1.5.3	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Race (Safety Analysis Set)	Yes	Yes
Table 14.3.1.5.4	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Geographic Region (Safety Analysis Set)	Yes	Yes
Table 14.3.1.5.5	Summary of Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- by Quantity of Product Used (Safety Analysis Set)	Yes	Yes
Table 14.3.1.6.1	Summary of OLP Treatment-Emergent Adverse Events – Overall Summary – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.2	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.3	Summary of OLP Treatment-Emergent Adverse Events by Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.4	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.5	Summary of OLP Serious Treatment-Emergent Adverse Events by Preferred Term – OLP Data (Safety Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.3.1.6.6	Summary of OLP Severe Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.7	Summary of OLP Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.8	Summary of OLP Serious Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.9	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.10	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.11	Summary of OLP Related Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.12	Summary of OLP Serious Related Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.13	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.14	Summary of OLP Treatment-Emergent Adverse Events Due to Wound Complications – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.15	Summary of OLP Treatment-Emergent Adverse Events based on the Adverse Event Onset and classified by the Duration of Treatment Exposure Intervals by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.1.6.16	Summary of OLP Treatment-Emergent Adverse Events Leading to Drug Withdrawal by System Organ Class and Preferred Term – OLP Data (Safety Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.3.1.7.1	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Age Group (Safety Analysis Set)	Yes	No
Table 14.3.1.7.2	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Gender (Safety Analysis Set)	Yes	No
Table 14.3.1.7.3	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Race (Safety Analysis Set)	Yes	No
Table 14.3.1.7.4	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Geographic Region (Safety Analysis Set)	Yes	No
Table 14.3.1.7.5	Summary of OLP Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Quantity of Product Used (Safety Analysis Set)	Yes	No
Table 14.3.1.8.1	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Age Group (Safety Analysis Set)	Yes	No
Table 14.3.1.8.2	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Gender (Safety Analysis Set)	Yes	No
Table 14.3.1.8.3	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Race (Safety Analysis Set)	Yes	No
Table 14.3.1.8.4	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Geographic Region (Safety Analysis Set)	Yes	No
Table 14.3.1.8.5	Summary of OLP Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term -- OLP Data -- by Quantity of Product Used (Safety Analysis Set)	Yes	No
Table 14.3.1.9.1	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Age Group (Safety Analysis Set)	Yes	No

Table Number	Table Title	DBP	OLP
Table 14.3.1.9.2	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Gender (Safety Analysis Set)	Yes	No
Table 14.3.1.9.3	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Race (Safety Analysis Set)	Yes	No
Table 14.3.1.9.4	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Geographic Region (Safety Analysis Set)	Yes	No
Table 14.3.1.9.5	Summary of OLP Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Quantity of Product Used (Safety Analysis Set)	Yes	No
Table 14.3.1.10.1	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Age Group (Safety Analysis Set)	Yes	No
Table 14.3.1.10.2	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Gender (Safety Analysis Set)	Yes	No
Table 14.3.1.10.3	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Race (Safety Analysis Set)	Yes	No
Table 14.3.1.10.4	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Geographic Region (Safety Analysis Set)	Yes	No
Table 14.3.1.10.5	Summary of OLP Serious Treatment-Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term -- OLP Data -- by Quantity of Product Used (Safety Analysis Set)	Yes	No
Table 14.3.2.1.1	Listing of Deaths (Safety Analysis Set)	Yes	Yes
Table 14.3.2.1.2	Listing of Serious Treatment-Emergent Adverse Events (Safety Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.2.1.3	Listing of Treatment Treatment-Emergent Adverse Events Leading to Study Withdrawal (Safety Analysis Set)	Yes	Yes
Table 14.3.2.2.1	Listing of OLP Deaths -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.2.2.2	Listing of OLP Serious Treatment-Emergent Adverse Events -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.2.2.3	Listing of OLP Treatment Treatment-Emergent Adverse Events Leading to Study Withdrawal -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.4.1.1.1	Summary of Hematology by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.1.2	Summary of Hematology – Shift Table by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.1.3	Summary of OLP Hematology by Visit -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.4.1.1.4	Summary of OLP Hematology – Shift Table by Visit -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.4.1.2.1	Summary of Biochemistry by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.2.2	Summary of Biochemistry – Shift Table by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.2.3	Summary of OLP Biochemistry by Visit -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.4.1.2.4	Summary of OLP Biochemistry – Shift Table by Visit -- OLP Data (Safety Analysis Set)	Yes	No
Table 14.3.4.1.3.1	Summary of Betulin Levels by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.2	Summary of Betulin Levels by Visit – by Age Group - (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.3	Summary of Betulin Levels by Visit – by Gender - (Safety Analysis Set)	Yes	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.4.1.3.4	Summary of Betulin Levels by Visit – by Baseline BMI - (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.5	Summary of Betulin Levels by Visit – by Baseline Total Wound Burden EBDASI Total Score - (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.6	Summary of Betulin Levels by Visit – by Baseline Total BSAP - (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.7	Summary of Betulin Levels by Visit – by Quantity of Product Used - (Safety Analysis Set)	Yes	Yes
Table 14.3.4.1.3.8	Summary of Betulin Levels by Visit – by Baseline Total Wound Area - (Safety Analysis Set)	Yes	Yes
Post-Hoc Table 14.3.4.1.3.9	Scatter Plot for Betulin Levels versus Age during DBP (Safety Analysis Set)	Yes	No
Post-Hoc Table 14.3.4.1.3.10	Scatter Plot for Betulin Levels versus BMI during DBP (Safety Analysis Set)	Yes	No
Post-Hoc Table 14.3.4.1.3.11	Scatter Plot for Betulin Levels versus Total Wound Area during DBP (Safety Analysis Set)	Yes	No
Table 14.3.4.1.4.1	Summary of OLP Betulin Levels by Visit -- OLP Data (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.2	Summary of OLP Betulin Levels by Visit -- OLP Data - by Age Group - (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.3	Summary of OLP Betulin Levels by Visit -- OLP Data - by Gender - (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.4	Summary of OLP Betulin Levels by Visit -- OLP Data - by Baseline BMI - (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.5	Summary of OLP Betulin Levels by Visit -- OLP Data - by Baseline Total Wound Burden EBDASI Total Score - (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.6	Summary of OLP Betulin Levels by Visit -- OLP Data - by Baseline Total BSAP - (Safety Analysis Set)	No	Yes
Table 14.3.4.1.4.7	Summary of OLP Betulin Levels by Visit -- OLP Data - by Quantity of Product Used - (Safety Analysis Set)	No	Yes

Table Number	Table Title	DBP	OLP
Table 14.3.4.1.4.8	Summary of OLP Betulin Levels by Visit -- OLP Data - by Baseline Total Wound Area - (Safety Analysis Set)	No	Yes
Post-Hoc Table 14.3.4.1.4.9	Scatter Plot for Betulin Levels - OLP Data - versus Age during OLP (Safety Analysis Set)	No	Yes
Post-Hoc Table 14.3.4.1.4.10	Scatter Plot for Betulin Levels - OLP Data- versus BMI during OLP (Safety Analysis Set)	No	Yes
Post-Hoc Table 14.3.4.1.4.11	Scatter Plot for Betulin Levels - OLP Data - versus Total Wound Area during OLP (Safety Analysis Set)	No	Yes
Table 14.3.4.2.1	Summary of Vital Signs by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.3.1	Summary of Electrocardiogram – Shift Table by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.4.1	Summary of Physical Examination by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.5.1	Summary of Local Tolerability by Visit (Safety Analysis Set)	Yes	Yes
Table 14.3.4.5.2	Summary of OLP Local Tolerability by Visit – OLP Data (Safety Analysis Set)	Yes	No

*** These outputs are required for Topline Results

16.2. INDEX OF LISTINGS

Listing Number	Listing Title	DBP	OLP
Listing 16.2.1.1	Patient Disposition (All Enrolled Patients)**	Yes	Yes
Listing 16.2.1.2	Patient Completion and Discontinuation by Study Phase (Safety Analysis Set)**	Yes	Yes
Listing 16.2.1.3	Site, Home, Telephone, Unscheduled Visits (All Enrolled Patients)**	Yes	Yes
Listing 16.2.2.1	Major Protocol Deviations (Safety Analysis Set)**	Yes	Yes
Listing 16.2.2.2	Major Protocol Deviations due to COVID-19 (Safety Analysis Set)**	Yes	Yes
Listing 16.2.2.3	Minor Protocol Deviations (Safety Analysis Set)	Yes	Yes
Listing 16.2.3.1	Patient Eligibility – Inclusion or Exclusion Criteria not Met (All Enrolled Patients)**	Yes	No
Listing 16.2.3.2	Exclusions from the Analysis Sets (All Enrolled Patients)	Yes	No
Listing 16.2.4.1	Demographics Data (Safety Analysis Set)**	Yes	Yes
Listing 16.2.4.2	Baseline Characteristics and Subgroup Variables (Safety Analysis Set)**	Yes	Yes
Listing 16.2.4.3	Medical History (Safety Analysis Set)	Yes	No
Listing 16.2.4.4	EB (Epidermolysis Bullosa) Subtype and EB Target Wound Selection (Safety Analysis Set)**	Yes	No
Listing 16.2.4.5	Prior and Concomitant Medications (Safety Analysis Set)**	Yes	Yes
Listing 16.2.5.1	Investigational Product Allocation at Randomization and during the Study (Safety Analysis Set)	Yes	Yes

Listing Number	Listing Title	DBP	OLP
Listing 16.2.5.2	Return of Study Medication (Safety Analysis Set)	Yes	Yes
Listing 16.2.5.3	Dressing Change and Study Medication Administration (Safety Analysis Set)**	Yes	Yes
Listing 16.2.5.4	Local Tolerability (Safety Analysis Set)**	Yes	Yes
Listing 16.2.5.5	Treatment Interruptions (Safety Analysis Set)**	Yes	Yes
Listing 16.2.5.6	Treatment Compliance (Safety Analysis Set)**	Yes	Yes
Listing 16.2.5.7	Local Tolerability – OLP Data (Safety Analysis Set)	Yes	No
Listing 16.2.6.1.1	Target Wound Photography (Safety Analysis Set)**	Yes	Yes
Listing 16.2.6.1.2	Closure of Wound(s) - Clinical Assessment (Safety Analysis Set)**	Yes	Yes
Listing 16.2.6.1.3	Closure of Wound(s) - Patient Assessment (Safety Analysis Set)**	Yes	No
Listing 16.2.6.2	Wound Infections (based on AEs and/or Use of Topical and/or Systemic Antibiotics – including AE Severity) (Safety Analysis Set)**	Yes	Yes
Listing 16.2.6.3	EB Disease Activity and Scarring Index (EBDASI) – Section 1 (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.4.1	Itch Man Scale – Patients >= 4 Years and up to 13 Years of Age - (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.4.2	Leuven Itch Scale – Patients >= 14 Years of Age – all Single Questions (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.4.3	Leuven Itch Scale – Patients >= 14 Years of Age – Subscores (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.5	Body Surface Area Percentage (BSAP) Affected by EB Partial Thickness Wounds (Safety Analysis Set)	Yes	Yes

Listing Number	Listing Title	DBP	OLP
Listing 16.2.6.6.1	FLACC Pain Rating Scale – Background Pain Before Dressing Change – Patients < 4 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.6.2	FLACC Pain Rating Scale – Procedural Pain After Dressing Change – Patients < 4 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.7.1	Wong-Baker Faces Pain Rating Scale - Background Pain Before Dressing Change – Patients >= 4 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.7.2	Wong-Baker Faces Pain Rating Scale -- Procedural Pain After Dressing Change – Patients >= 4 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.8	Impact of Wounds on Sleep (W-QoL) – Patients >= 14 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.9	Days Missed from School or Work (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.10	Treatment Satisfaction Questionnaire for Medication (TSQM) – Before Dressing Change – Patients >= 14 Years of Age (Safety Analysis Set)	Yes	Yes
Listing 16.2.6.11	Disease Severity (IscorEB) - Clinician Subscore (Safety Analysis Set)	No	Yes
Listing 16.2.6.12	Disease Severity (IscorEB) - Patient Subscore (Safety Analysis Set)	No	Yes
Listing 16.2.6.13	Disease Severity (IscorEB) – Total iscorEB Score (Safety Analysis Set)	No	Yes
Listing 16.2.6.14	Health-related Quality of Life (EQ-5D) (Safety Analysis Set)	No	Yes
Listing 16.2.7.1	Adverse Events (Safety Analysis Set)**	Yes	Yes
Listing 16.2.7.2	OLP Adverse Events – OLP Data (Safety Analysis Set)**	Yes	No
Listing 16.2.8.1.1	Hematology (Safety Analysis Set)**	Yes	Yes
Listing 16.2.8.1.2	Biochemistry (Safety Analysis Set)**	Yes	Yes

Listing Number	Listing Title	DBP	OLP
Listing 16.2.8.1.3	Pregnancy Test (Safety Analysis Set)**	Yes	Yes
Listing 16.2.8.1.4	Betulin Collection and Results (Safety Analysis Set)**	Yes	Yes
Listing 16.2.8.1.5	Suspected EB Wound Infection – Result of Swab Test (Safety Analysis Set)**	Yes	Yes
Listing 16.2.8.1.6	Hematology – OLP Data (Safety Analysis Set)	Yes	No
Listing 16.2.8.1.7	Biochemistry – OLP Data (Safety Analysis Set)	Yes	No
Listing 16.2.8.2	Vital Signs (Safety Analysis Set)	Yes	Yes
Listing 16.2.8.3	Electrocardiogram (Safety Analysis Set)	Yes	Yes
Listing 16.2.8.4	Physical Examination (Safety Analysis Set)	Yes	Yes

** These outputs are required for the Blind Data Review Meeting.

17. APPENDIX 1: PROHIBITED WOUND DRESSING/CONTACT LAYERS

Nonpermitted dressings/contact layers	DBP	OLP	Reason
Containing emollients			
Adaptic™	X	-	Contains petrolatum
Atrauman®	X	-	Polyester tulle impregnated with fatty acids
Branolind	X	-	Contains petrolatum
Cuticell®	X	-	Paraffin gauze
Cuticerin	X	-	Acetate gauze impregnated with CUTICERIN ointment
Grassolind®	X	-	Contains vaseline
Jelonet	X	-	Contains paraffine
Licotul Optimelle	X	-	Contains paraffine
Linitul	X	-	Contains petrolatum, paraffine
Paraffine dressing	X	-	Contains paraffine
Physiotulle	X	-	Contains vaseline
UrgoTul	X	-	Impregnated with petroleum jelly
Vaseline gauze	X	-	Contains vaseline
Containing active ingredients			
Kerlix™ AMD	X	X	Contains PHMB
Mepilex AG	(X)	(X)	Contains silver; only permitted in single other wounds[a] or in target/additional wounds after complete closure and confirmed epithelialization
Telfa™ AMD	X	X	Contains PHMB
UrgoTul Ag	X	(X)	Contains silver; only permitted in single other wounds[a] or in target/additional wounds after complete closure and confirmed epithelialization
Xeroform	X	-	Contains petrolatum and 3% bismuth tribromophenate
Adherent dressing			
Gauze pads	X	X	Adherent

Abbreviations: Ag=argentum (silver); PHMB=polyhexamethylene biguanide

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