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

EASE Study

Investigational product	Oleogel-S10		
Indication	Inherited epidermolysis bullosa (EB)		
Identifier	EudraCT No. 2016-002066-32		
Study number	BEB-13		
Development phase	III		
Document	Study Protocol BEB-13		
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Author(s) [redacted]

Compliance The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable federal and local regulations.

Sponsor **Amryt Research Limited**
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SIGNATURE PAGE

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INVESTIGATOR'S AGREEMENT

I have read and understood the protocol and agree with its content.

I will conduct the study in compliance with the protocol, Good Clinical Practice, national law, and all applicable regulatory requirements. In addition, I will conduct the study in accordance with the ethical principles of the Declaration of Helsinki.

I am familiar with the nonclinical and clinical data of the investigational drug and with its known and potential benefits and risks.

I agree to assume responsibility for the proper conduct of the study at this site and I will ensure that all persons assisting in the study under my supervision are adequately informed about the protocol/amendments, the investigational product and their study-related duties and functions as described in the protocol.

I will not implement any deviation from, or changes to the protocol without agreement from Amryt Research Ltd. and prior submission to and written approval from the responsible regulatory authorities and Independent Ethics Committee/Institutional Review Board of an amendment, except when necessary to eliminate an immediate hazard to the patients.

I understand that either Amryt Research Ltd. or myself may terminate the study or may suspend enrolment at any time, if it becomes necessary to protect the patients' best interest.

Name _____

Address _____

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_____ _____

Place, Date Signature

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LIST OF TERMS AND ABBREVIATIONS

Term or Abbreviation	Description
AE	Adverse event
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BG	Blood glucose
BSAP	Body surface area percentage
Ca	Calcium
CCC	Confirmation of complete closure (of EB target wound)
CHW	Cui, Hung, Wang
CI	Confidence interval(s)
Cl	Chloride
CMH	Cochran-Mantel-Haenszel
COL7A1	Collagen VII
CTCAE	Common Terminology Criteria for Adverse Events
D	Day(s)
DBP	Double-blind phase
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
DEJZ	Dermal-epidermal junction zone
DS	Donor site
EB	Epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDBP	End of Double-blind Phase
EoFU	End of Follow-up
EQ-5D	EuroQol 5 Dimensions
FAS	Full analysis set
FDA	Food and Drug Administration
FLACC	Face, Legs, Activity, Cry, Consolability
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
I	Investigator
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Term or Abbreviation	Description
iscorEB	Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa
JEB	Junctional epidermolysis bullosa
K	Potassium
M	Month(s)
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing not at Random
Na	Sodium
P	Phosphate
PP	Per-protocol (analysis set)
PRO	Patient-reported outcome
Pt	Patient
Q	Quarter
RDEB	Recessive dystrophic epidermolysis bullosa
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SOC	Standard of care
STSG	Split-thickness skin graft
SUSAR	Suspected unexpected serious adverse reaction
TBSA	Total body surface area
TSQM	Treatment Satisfaction Questionnaire for Medication
V	Visit
W-QoL	Wound Quality of Life Questionnaire

1 SUMMARY OF CLINICAL STUDY

1.1 Study Synopsis

Title of study

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

Sponsor

Amryt Research Ltd, 90 Harcourt Street, Dublin 2, Ireland

Coordinating investigator

[redacted] The Royal Melbourne Hospital, Department of Dermatology, 300 Grattan St, Parkville VIC 3050, Australia

Study centres

Global multicentre study with approximately 50 study sites

Countries

Argentina, Australia, Austria, Belgium, Brazil, Chile, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Romania, Russia, Serbia, Singapore, Spain, Switzerland, United Kingdom, United States of America and more are planned

Phase of development

Phase III

Number of patients

Planned enrolment (original study design): N=192

Planned enrolment (following unblinded interim analysis): N = 250

Patients will be randomised to treatment in a 1:1 ratio to receive Oleogel-S10 or vehicle

Study objectives

Primary objective

- The primary objective of the double-blind phase (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 will be 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 EB [JEB], dystrophic EB [DEB], or Kindler syndrome) within 45±7 days of treatment.

Secondary objectives – double-blind phase

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

Objectives – open-label follow-up phase

The objectives of the 24-month open-label follow-up (FU) phase are to:

- 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 Month 3 (M3) ±14 days
- Assess the changes from baseline of both DBP (Day 0 [D0]) and the FU (D0)/end of DBP (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 FU (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 FU (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 FU (D0)/EDBP (D90±7) in itch before wound dressing changes at M3±14 days
- Assess the changes from baseline of both DBP (D0) and FU (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 FU (D0)/EDBP (D90±7) in treatment response (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

Endpoints for double-blind phase

Primary efficacy endpoint

- 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 (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 will be rated as "closed" at first appearance of complete reepithelialisation without drainage)

Key secondary (confirmatory) efficacy endpoints

- Time to first complete closure of the EB target wound as evidenced by clinical assessment until EDBP (D90±7)
- Proportion of patients with first complete closure of the EB target wound at D90±7 based on clinical assessment by the investigator
- 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)
- 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)
- 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) at D90±7
- 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

Other secondary efficacy endpoints

- 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
- 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
- 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
- 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
- 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) at D30±7 and D60±7
- 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 at D30±7, D60±7, and D90±7
- Change from baseline (DBP D0) in "background" pain using the '*Face, Legs, Activity, Cry, Consolability*' (FLACC) pain rating 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, and D90±7
- Change from baseline (DBP D0) in "procedural" pain 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, and D90±7
- 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 D7±2, D30±7 and D60±7
- 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
- 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
- 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

Safety endpoints

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Systemic exposure to betulin

Endpoints for open-label follow-up phase (Oleogel-S10 for 24 months after completion of randomised treatment)

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Systemic exposure to betulin
- Proportion of patients with first complete closure of the EB target wound at M3±14 days based on clinical assessment by the investigator and blinded evaluation of photographs
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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 at M3±14 days, M12±14 days, and at End of Follow-up (EoFU) at M24±14 days
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in BSAP of TBSA affected by EB partial thickness wounds as evidenced by clinical assessment based on the '*Lund and Browder*' chart at M3±14 days, M12±14 days, and at EoFU at M24±14 days
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in "background" pain 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

- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in "procedural" pain 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
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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 M3±14 days
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in impact of wounds on sleep (in patients ≥ 14 years of age) as measured by differences in 11-point Likert scales at M3±14 days
- 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 response (in patients ≥ 14 years of age) using the TSQM, Version 9, before wound dressing changes at M3±14 days
- 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 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

Study design

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). At the EDBP (Visit 7a on D90±7), patients in both treatment arms will enter the single-arm, open-label FU phase with Oleogel-S10 for 24 months. The randomised DBP will consist of 3 periods; the open-label FU phase will comprise 1 period as described below.

Double-blind phase:

1. Screening (up to 28 days prior to baseline)

   Study sites contact and invite patients registered in centre-specific databases. Patients who fail screening may be rescreened if he/she later becomes eligible, as deemed appropriate by the investigator.
2. Baseline, enrolment and stratified randomisation (D0)

   The investigator will confirm eligibility for the patient on D0 corresponding to the study flow chart, check the eligibility criteria, select the EB target wound, and enrol the patient into the study. Patients will be stratified according to their EB subtype and target wound size (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 will then be randomised 1:1 to receive either Oleogel-S10 (treatment arm A) or vehicle (treatment arm B).
3. Intervention (90 days±7 days)

   The treatment of the EB partial thickness target wound and all areas on the patient's body that are affected by EB partial thickness wounds with Oleogel-S10 and a standard of care (SOC) non-adhesive wound dressing (treatment arm A) or with vehicle and an SOC non-adhesive wound dressing (treatment arm B) will start the same day (D0).

Safety and local tolerability will be monitored and documented continuously throughout the study.

24-month open-label follow-up phase:

Once the EDBP visit for the randomised DBP has been completed and the return of the corresponding unused study medication (Oleogel-S10 or vehicle gel) has occurred, the patient will enter the single-arm, open-label, 24-month FU phase. The EDBP visit at D90±7 (Visit 7a) corresponds to first visit (D0) of the FU phase (Visit 7b). The data of total body wound burden and BSAP assessment at EDBP (D90±7) will be used as baseline data of D0 of the FU phase.

All patients will start topical Oleogel-S10 administration on D0 of the FU phase to all areas on the patient's body that are affected by EB partial thickness wounds including the EB target wound. Wound areas will be covered with SOC non-adhesive wound dressing. This procedure will be repeated during all dressing changes based on the study flow chart (at least every 4 days) until the end of treatment at M24±14 days.

Study population

Inclusion criteria

A patient will be eligible for study participation only if all of the following criteria apply:

1. Male and female patients age ≥ 4 years with the following subtypes of inherited EB: JEB, DEB, and Kindler syndrome

Note: Children ≥ 21 days old and <4 years may be included only after confirmation by the Independent Data Monitoring Committee (IDMC) upon review of the safety and bioanalytical data at the interim safety review stage

2. Patients with an EB target wound (i.e., EB partial thickness wound of 10 cm^2 to 50 cm^2 in size, aged ≥ 21 days and <9 months) outside of the anogenital region
3. Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed consent
4. Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions

Exclusion criteria

A patient will not be eligible to participate in this study if any of the following criteria apply:

1. Patient has EB subtype EB simplex
2. EB target wound that is ≥ 9 months old or has clinical signs of local infection
3. Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment
4. Administration of systemic or topical steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL]) within 30 days before enrolment
5. Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment
6. Patient has undergone stem cell transplant or gene therapy for the treatment of inherited EB
7. Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas
8. Enrolment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry
9. Factors present in the patient and/or his/her legal representative that could interfere with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes
10. Pregnant or nursing women
11. Women of childbearing potential, including postmenarchal female adolescents, and men who are not willing to use an effective form of birth control with failure rates <1% per year (e.g., implant, injectable, combined oral contraceptive, intrauterine contraceptive device, sexual abstinence, vasectomy or vasectomised partner) during participation in the study (and at least 3 months thereafter)
12. Patient is a member of the investigational team or his/her immediate family
13. Patient lives in the same household as a study participant

Treatment plan

Investigational product

100 g of the investigational product Oleogel-S10 consists of 10 g active pharmaceutical ingredient birch bark extract and 90 g sunflower oil

Placebo/Control

100 g of the sterile vehicle gel will consist of 85 g sunflower oil, 5 g Cera flava/yellow wax, and 10 g Carnauba wax

Standard of care non-adhesive wound dressing

Standard of care non-adhesive wound dressings are defined as modern non-adhesive wound dressings such as Mepitel® (Mölnlycke Health Care AB, Sweden) or PolyMem® (Ferris Mfg. Corp., USA) or equivalents. Silver dressings and dressings containing topical emollients (e.g. vaselinized gauze) are not allowed.

Dosage and mode of administration

Double-blind, randomised phase:

The study medication will be administered topically at approximately 1 mm (0.04 inch) thickness to the EB target wound and to all areas on the patient's body that are affected by EB partial thickness wounds. Wound areas will then be covered with an SOC non-adhesive wound dressing. Alternatively, the study medication may be applied to the dressing first and the medication-covered dressing then placed on the wound. This procedure will be repeated during all dressing changes based on the study flow chart (at least every 4 days) until the EDBP at D90±7. The study medication should not be rubbed into the wounds. The study medication should not be mixed with other skin products such as creams, ointments, gels, or emollients or applied with such skin products at the same time. The investigator may implement a dose interruption if considered medically necessary for optimal management of the patient. Dose interruptions are not allowed for using non-permitted concomitant medication to treat worsening of wound status, increase in wound size, and wound infections of EB target wounds and other wounds matching target wound criteria. For worsening of the EB target wound status or EB target wound infections the patient may discontinue the DBP and enter the FU phase prematurely. Should any other interruptions of treatment occur, the investigator should be contacted immediately. Areas on the patient's body that are not affected by EB partial thickness wounds are not to be treated with the study medication. If the EB target wound (or other wound matching target wound criteria) closes during the study, it is not necessary to apply study medication to the closed wound. The study medication is not intended for use on full thickness wounds (i.e., entire dermis, extend into the subcutis) in this study.

Open-label follow-up:

Open-label treatment with Oleogel-S10 during the FU phase until the end of treatment at M24±14 days corresponds to the dosage and mode of administration as described above.

Concomitant treatment/medication

Permitted concomitant treatment/medication

- Liquid antiseptics such as polyhexanide, iodine products, or octenidine dihydrochloride at each wound dressing change to clean the EB target wound (and other wounds matching target wound criteria) and/or to reduce microbial colonisation of the EB target wound (and other wounds matching target wound criteria) prior to study treatment
- Bathing (e.g., with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change
- Systemic antibiotics except for treatment of EB target wound (and other wounds matching target wound criteria) infections
- Inhaled, ophthalmic, or topical steroids, such as budesonide suspension for oesophageal strictures (e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL)
- Supportive therapy upon the investigator's discretion

On single EB wounds (except for the EB target wound and other wounds matching target wound criteria) during both the DBP and FU phase of the study:

- Silver sulfadiazine
- Topical antibiotics
- Topical steroids

Non-permitted concomitant treatment/medication

The following medication will not be permitted during the study until M3±14 days of the open-label FU:

- Systemic steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL])
- Immunosuppressive therapy or cytotoxic chemotherapy
- Systemic antibiotics to treat EB target wound (and other wounds matching target wound criteria) infections

On areas on the patient's body that are affected by EB wounds, the following medication will not be permitted during the DBP of the study:

- Skin products such as creams (including barrier creams), ointments (and dressings containing topical emollients e.g. vaselinized gauze), gels, or emollients

On the EB target wound (and other wounds matching target wound criteria), the following medication will not be permitted until complete closure and confirmed epithelialisation during both the DBP and FU phase of the study:

- Silver dressings
- Silver sulfadiazine
- Topical antibiotics

Topical steroids

Duration of patient participation in the study

Each patient will participate for 90±7 days in the randomised DBP (approx. 3 months). Each patient in the open-label FU phase will receive Oleogel-S10 treatment for 24 months. The total study duration (DBP and open-label FU phase) will be approximately 27 months.

Timelines of randomised, double-blind phase

- Estimated date of first patient enrolled: Quarter (Q)1/2017
- Estimated date of last patient enrolled: Q3/2019
- Estimated date of last patient EDBP: Q4/2019

Timelines of open-label, follow-up phase

- Estimated date of last patient EoFU treatment: Q4/2021

Number of visits (DBP)

- Six visits at the study site at D0, D14±5, D30±7, D45±7, D60±7, and D90±7 (EDBP) (for visits at D14±5 and at D45±7; alternatively, it is possible that the investigator visits patients at home)
- Two additional study site visits or study team member visits at home at D7±2 and 7 days (+2 days) after first clinical assessment of complete target wound closure for confirmation of complete closure (of the EB target wound). D7±2 can also be a phone call instead of a site or home visit.

Number of visits (open-label, follow-up phase)

- Three visits at the study site at M3±14 days, M12±14 days, and M24±14 days (EoFU).
- Five interim phone calls at M6±28 days, M9±28 days, M15±28 days, M18±28 days, M21±28 days. A site visit may be scheduled instead of an interim phone call to facilitate dispensing of study medication.

Patient discontinuation criteria

Patients and/or his/her legal representatives will have the right to withdraw from the study at any time for any reason without prejudice to their future medical care.

The investigator will also be able to withdraw patients from the study for the following reasons:

- Worsening of the EB target wound status or EB target wound infection as assessed by the investigator
- Patient is non-compliant with the study procedures or medications in the opinion of the investigator
- Progression of a medical condition, which in the opinion of the investigator should preclude further participation of the patient in the study
- Administration of non-permitted concomitant medication(s)
- Investigator's decision that a change of therapy is in the patient's best interest
- Occurrence of an AE, which makes discontinuation desirable or necessary in the investigator's and/or the patient's opinion

  If a patient discontinues the DBP or the FU prematurely due to an AE/serious AE (SAE), every effort will be made to follow the patient until the resolution of the AE/SAE. If a patient discontinues the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection, the investigator may decide whether the patient enters the FU prematurely or discontinues the study completely.
- Pregnancy as evidenced by a positive pregnancy test

  If a patient or the partner of a male patient becomes pregnant during the study, during the FU phase, or 30 days within the last application of study medication, the sponsor must be informed within 24 hours. The investigator will be asked to complete a pregnancy report provided by the sponsor. The investigator will be asked to obtain data on the course of the pregnancy, including perinatal and neonatal outcome up to 28 days after delivery.

Independent Data Monitoring Committee

An IDMC will be established to review and evaluate primary efficacy and safety data during the DBP of the study. The board will consist of independent experts who will not be involved in the study. The safety review will be performed blinded and is to ensure safety for participants, and to advise for continuation, modification or discontinuation of individual patients and/or of the study. Following an unblinded interim safety review, the IDMC will be able to confirm if the study can be expanded to allow the inclusion of children with EB to all ages (i.e., ≥ 21 days and < 4 years).
The unblinded interim analysis for sample size re-estimation will take place when approximately 50% of patients have completed D45±7. Depending on the results of the sample size re-estimation, the IDMC will recommend to continue with the initial sample size, increase the sample size, or stop the study for futility.

Statistical methods

Sample size of the study

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 test of equality of binomial proportions at the alpha=0.05 level of significance, a total sample size of 182 subjects (91 subjects per arm) will provide 80% power to detect an improvement of 20 percentage points (i.e., a true Oleogel-S10 rate of 47%). A total of 192 patients are planned to be enrolled into the study and treated to account for an estimated drop-out rate of 5%.

Following the unblinded interim analysis, the IDMC recommended to have a sample increase of 48 patients (24 per arm) to have a total of 230 subjects. A total of 250 patients are planned to be enrolled into the study and treated to account for drop-outs.

Confirmatory statistical testing

The primary efficacy endpoint and the key secondary efficacy endpoints will be tested in a confirmatory way, following the hierarchical testing principle.

1.2 Flow Chart of Study (Randomised, Double-blind and Open-label Follow-up)

Examination	Screening	Randomised, Double-blind Phase						Open-label Follow-up Phase			
			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)	D0	D7±2d[B]	CCC[C]	D14±5d[D]/ D45±7d[D]	D30±7d / D60±7d	EDBP (D90±7d) / FU (D0)[E]	M3 (±14d)	M12 (±14d)	M6, M9, M15, M18, M21 (±28d)	EoFU 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			
▪ 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			

Examination	Screening	Randomised, Double-blind Phase						Open-label Follow-up Phase			
			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)	D0	D7±2d[B]	CCC[C]	D14±5d[D]/ D45±7d[D]	D30±7d / D60±7d	EDBP (D90±7d) / FU (D0)[E]	M3 (±14d)	M12 (±14d)	M6, M9, M15, M18, M21 (±28d)	EoFU M24(±14d)
Visit	--	1	2	+	3/5	4/6	7a/7b	8	9	--	10
▪ Photography of other wounds matching target wound criteria		X	X[I]		X	X	X	X			
▪ Closure of target wound (clinical assessment) [L]				X[L]	X	X	X	X			
▪ Closure of target wound (patient assessment)			X		X	X	X				
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, a bumin, 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									
▪ 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 FU phase, respectively									

AE = Adverse event; ALT = Alanine aminotransferase; AP = A kaline 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; EoFU = End of Follow-up; 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 open-label follow-up phase (FU [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 will be 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 will be performed if patient has site visit or home visit at D7±2. If the patient has phone call, the assessment will not be performed.
J. “Background” pain will be measured before dressing change; “procedural” pain will be 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 will continue to be applied to any other EB partial thickness wounds.

2 INTRODUCTION

2.1 Background

2.1.1 Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a rare ('orphan'), heterogeneous group of genetic skin fragility disorders characterised by blistering of the skin in response to minor trauma or friction.

Based on data of the US National EB registry, the prevalence of EB was estimated as 8 per 1 million population in 1990 and the incidence was 19 per 1 million live births between 1986 and 1990 without any predilection by gender or ethnicity (Fine 2010).

EB is caused by more than 1,000 known mutations in 18 genes encoding anchoring proteins of the dermo-epidermal junction (Bruckner-Tuderman and Has 2012, Schwieger-Briel, Chakkittakandiyil et al. 2015). Defects of these proteins lead to different levels of cleavage within the skin according to their location in the dermo-epidermal junction (Fine 2010).

In 2014, a revised EB consensus classification was published. It divides EB into 4 major categories, based on the level of skin cleavage (Fine, Bruckner-Tuderman et al. 2014):

1. EB simplex (EBS; intraepidermal skin separation)
2. Junctional EB (JEB; skin separation within the lamina lucida or central basement membrane zone)
3. Dystrophic EB (DEB; sublamina densa or dermal separation)
4. Kindler syndrome (variable level of separation in the skin within basal keratinocytes, at the level of the lamina lucida or below the lamina densa)

In most cases, onset of EB is at birth or shortly after. Disease severity differs greatly depending on the type of EB: EBS causes mild to moderate disease with limited blistering and little or no extracutaneous involvement (see Figure 1 a). In 2002, the prevalence of EBS was 6.00 per 1 million live births (Fine 2016).

Figure 1 Wounds in Epidermolysis Bullosa by Subtype

a. Epidermolysis Bullosa Simplex *Heel-prick blistering*

b. Junctional Epidermolysis Bullosa *Hand blistering*

c. Dystrophic Epidermolysis Bullosa *Chronic neck blistering*

Source: (Pope, Lara-Corrales et al. 2011)

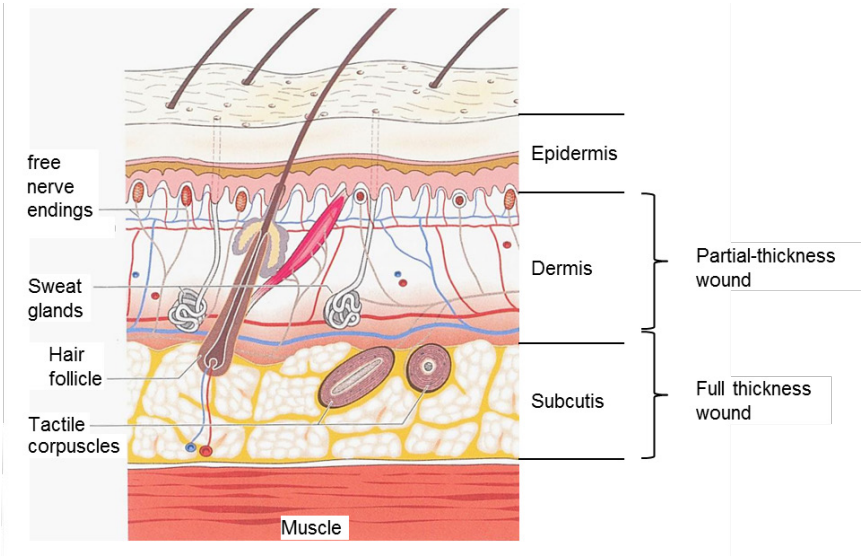
JEB has a broad spectrum of severity from the lethal form of generalised severe JEB with an estimated mortality rate of 87% during the first year of life to very mild forms often diagnosed later on (see Figure 1 b) (Fine, Johnson et al. 2008). In 2002, the prevalence of JEB was 0.49 per 1 million live births (Fine 2016). The majority of patients encountered in specialised centres suffer from DEB, which causes moderate to severe skin fragility and scarring. Severely affected patients suffer from widespread blistering and painful wounds often resulting in physical impairment (see Figure 1 c) (Bruckner-Tuderman 2010). In 2002, the prevalence of dominant DEB (DDEB) was 1.49 per 1 million live births, the prevalence of recessive DEB (RDEB) was 1.35 per 1 million live births, and the prevalence of DEB (unknown mode) was 0.42 per 1 million live births (Fine 2016). Hallmark of most EB

subtypes is skin blistering with associated recurrent and persistent wounds (Schwieger-Briel, Chakkittakandiyil et al. 2015).

2.1.2 Epidermolysis Bullosa Partial Thickness Wounds

Human skin consists of 3 layers comprising epidermis, dermis, and subcutis (see Figure 2). The epidermis serves as a barrier to infection. The dermis underneath contains the skin appendages, sensory nerve receptors, nails, and blood vessels. A thin sheet of fibres called the basement membrane separates epidermis and dermis. Basal keratinocytes of the stratum basale that continuously regenerate the epidermis are located above the basement membrane. Keratinocytes mature, differentiate, and progress through the layers of the epidermis in a life cycle lasting approximately 3 to 4 weeks before being shed as corneocytes. Keratinocytes are of paramount importance for the reepithelialisation of partial thickness wounds (Doughty 2012).

Figure 2 Human Skin and Depths of Cutaneous Wounds



Source: (Vogt and Ipaktchi 2013)

Wounds of the skin are classified into partial or full thickness wounds based on the depth of skin layers involved (see Figure 2). Partial thickness wounds involve loss of the epidermis and extend into the dermis. The basement membrane is lost, but skin appendages remain. Keratinocytes and epidermal stem cells in these dermal appendages are able to regenerate the epidermis within 1 to 3 weeks with minimal or no scarring. Full thickness wounds involve the entire dermis, extend into the subcutis and are not able to heal spontaneously within 3 weeks.

Partial thickness wounds are very painful, because sensory nerve endings are abundant in the remaining dermal tissue of the wound bed. In addition, there is an increased risk of infection due to the compromised skin barrier.

Many wounds in EB might be classified as partial thickness wounds, as the level of skin cleavage in the major 4 EB subtypes extends at maximum into the dermis. The total body wound burden of EB partial thickness wounds has a decisive effect on the quality of life, as it relates to pain, itching, and the complexity of wound care.

Fine and colleagues assessed pain in children with EB and reported that only 12 to 14% of children with EBS, JEB, and DDEB and 5% of children with RDEB were pain-free (Fine, Johnson et al. 2004).

Danial et al. evaluated the prevalence of itch among children and adults with EB. Itch was rated as the most bothersome EB complication. Overall, 87% of participants reported itch to

be present at rest. The average itch frequency increased with self-reported EB severity and was highest in RDEB patients and lowest in EBS patients (p=0.01). EB patients with ≥ 3 wound locations had a significantly higher frequency of pruritus than patients with < 3 wounds (p<0.001). Pruritus was strongest in healing wounds (p<0.001), skin around wounds (p<0.001), dry skin (p=0.001), and infected wounds (p=0.002) (Danial, Adeduntan et al. 2015).

Repeated infections, constant trauma and comorbidities such as compromised nutrition and anaemia are reasons for developing chronic wounds (Denyer and Pillay 2012). Infected and chronic wounds belong to the most frequent complications in the generalised intermediate and severe forms of EB (El Hachem, Zambruno et al. 2014). The most commonly isolated microorganisms in wound cultures from EB patients encompass *Staphylococcus* sp., *Streptococcus* sp., diphtheroids, *P. aeruginosa*, and *Candida* sp.; the presence of ≥ 4 bacterial groups is associated with significant delayed wound healing (Brandling-Bennett and Morel 2010).

Health care professionals and patients with EB were asked for their perception of disease severity as basis for the development of the '*Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa*' (iscorEB). '*Skin*' was the category most commonly listed by health care professionals with '*affected body surface area*', '*frequency of infections*', and '*chronic wounds*' being the most frequent items. Comparably, '*pain*' and the '*extent and healing of wounds*' were the most common items listed by patients (Schwieger-Briel, Chakkittakandiyil et al. 2015).

In summary, disease burden of EB across all subtypes closely relates to the total body surface area (TBSA) of EB partial thickness wounds with complications such as infections and symptoms such as pain and itching.

2.1.3 Treatment Options and Medical Need

In spite of the progress in aetiopathogenetic research of EB, there is still no cure or effective treatment for this group of potentially severe and fatal diseases (Uitto, McGrath et al. 2010, Hunefeld, Mezger et al. 2013). While there is a broad research effort searching for the best molecular strategies to ameliorate or treat EB (Hunefeld, Mezger et al. 2013), the knowledge on symptomatic and preventive wound care in EB is still limited by the paucity of scientific evidence with most recommendations based on expert opinion (Pope, Lara-Corrales et al. 2012).

Wound management in EB primarily depends on the subtype of the disease and on the age of the patient. The nutritional status, the general state of health, the current condition of the skin, the availability of wound dressings, optional involvement of nursing care at home, and the domestic environment also play important roles. The general principles of wound care are similar across all EB subtypes, but might differ markedly regarding intensity and effort (Diem and Sailer 2012).

There is no standard wound care in EB. Wound dressings are changed about every second day. Adherent wound dressings are soaked with lukewarm water in a bath or during a shower and with damp compresses, respectively. Creams or ointments are administered on those wounds that tend to adhere to the wound dressings. In case wounds are still not clean after taking a bath or a shower, small amounts of antiseptics are used before creams, ointments, and wound dressings are administered.

In moist wounds, rather searing creams are preferred. In dry, crusty wounds, greasing or moist creams are recommended. Infected, malodorous wounds are treated with antimicrobial creams for a maximum of 2 to 4 weeks. Antiseptic baths or antibiotic ointments might be used instead. Wounds that are difficult to be dressed might be treated with ointments containing zinc to dry out opened blisters. If a cream or an ointment is necessary, it might be administered directly to the wound or to the wound dressing that is applied to the wound (Diem and Sailer 2012).

Care of the skin currently not affected by superficial wounds is of major importance, particularly in dry skin (Diem and Sailer 2012). The use of topical emollients including moisturisers for skin care is widely recommended (Denyer and Pillay 2012, El Hachem, Zambruno et al. 2014). Equal parts of liquid paraffin and white soft paraffin are also used for (periwound) skin care (Denyer and Pillay 2012). Overall, greasy ointments (e.g., Vaseline®) are used most frequently, particularly for the management of pruritus. EB patients who used creams (p=0.05) or lotions (p=0.04) reported to experience less pruritus than those who used them less often (Danial, Adeduntan et al. 2014).

A wide range of oral medications is used for the treatment of pruritus including antihistamines (e.g., hydroxyzine, cetirizine, diphenhydramine), corticosteroids, antiepileptics (e.g., gabapentin), tricyclic antidepressants (e.g., doxepin, amitriptyline), serotonin 5-HT3 receptor antagonists (e.g., ondansetron), and benzodiazepines. For the treatment of severe recalcitrant itch, even thalidomide and cyclosporine are used. However, pruritus in EB is not mediated by histamine. Therefore, antihistamines are of limited value and are rather administered because of their sedating effect (Denyer and Pillay 2012).

Pain is relieved by the administration of non-steroidal anti-inflammatory analgesics and opioids depending on individual needs and the severity, chronicity and location of discomfort (Pillay 2008).

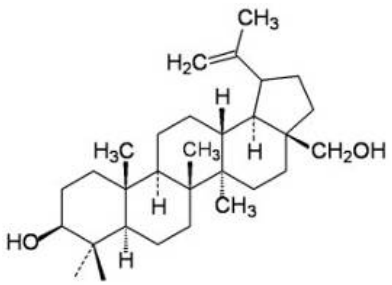
In summary, current treatment of EB is primarily preventive including protection from mechanical forces by avoiding friction, early treatment of lesions to prevent superinfections, and protection of the wound with adequate non-adhesive dressings to enable wound healing. Supportive care relieves itch and pain (Denyer and Pillay 2012, Pope, Lara-Corrales et al. 2012).

The acceleration of wound healing would meet an important medical need, as it would reduce pain, itch, and the risk of wound infection.

2.2 Investigational Product

Oleogel-S10 is a wound gel containing 10 g/100 g extract (as dry extract, refined) from *Betulae* cortex (birch bark) from *Betula pendula* Roth, *Betula pubescens* Ehrh, as well as hybrids of both species (5-10:1), quantified to 72% (w/w) to 88% (w/w) betulin (see Figure 3), extraction solvent n-heptane, and refined sunflower oil 90 g/100 g. Additional specified components of birch bark extract are betulinic acid, lupeol, oleanolic acid, and erythrodiol.

Figure 3 Molecular Structure of Betulin, the Active Pharmaceutical Ingredient of Oleogel-S10



Amryt Pharma Figure

Betulin = 3β,28-Dihydroxylup-20(29)-ene, Chemical Abstracts Service (CAS) number 473-98-3
Molecular formula: $C_{30}H_{50}O_2$; Molecular weight: 442.72 g/mol

Oleogel-S10 is a "preparation for treatment of wounds and ulcers" according to the Anatomical Therapeutic Chemical (Classification System [Anatomical Therapeutic Chemical code D03AX13 Betulae cortex]). It was approved under the trade name Episalvan® on 14 January 2016 in the European Union (EU/1/15/1069) for the treatment of partial thickness

wounds in adults after having demonstrated efficacy and safety in split-thickness skin graft (STSG) donor site (DS) wounds and in Grade 2a burn wounds.

2.3 Summary of Non-clinical Studies with Oleogel-S10

Woelfle and colleagues demonstrated that birch bark extract promotes the differentiation of keratinocytes, a process required for the reepithelialisation and maintenance of the skin barrier (Woelfle, Laszczyk et al. 2010). Ebeling and colleagues have shown in human primary keratinocytes that birch bark extract and betulin modulate various mediators involved in the inflammatory phase of the wound healing process. Birch bark extract increased the cell migration of primary human keratinocytes and accelerated wound closure in an *ex vivo* porcine wound healing model (Ebeling, Naumann et al. 2014).

Wardecki et al. investigated the impact of birch bark extract, betulin, and lupeol on primary human keratinocytes and fibroblasts from non-diabetic and diabetic donors *in vitro.* They have demonstrated an upregulation of chemokines, proinflammatory cytokines, and mediators important in wound healing and a shape change of the actin cytoskeleton in both keratinocytes and fibroblasts (Wardecki, Werner et al. 2016).

Furthermore, for triterpenes present in birch bark extract, namely betulin, betulinic acid and oleanolic acid, antiviral, antibacterial, antimycotic, anti-inflammatory, and antitumoral effects have been described (Galgon, Wohlrab et al. 2005, Alakurtti, Makela et al. 2006, Lee, Nam et al. 2006, Suksamrarn, Panseeta et al. 2006).

2.3.1 Non-clinical Evidence for Acceleration of Reepithelialisation in Inherited Epidermolysis Bullosa

The pathogenesis of blistering differs by EB subtype and the mechanisms of impaired wound healing are not fully delineated in all subtypes. Oleogel-S10 counteracts mechanisms of delayed wound healing downstream and it is assumed that these effects are relevant for all EB subtypes. Hemidesmosome protein complexes are not only involved in stable adhesion, but also regulate signal pathways in migrating cells (Tsuruta, Hashimoto et al. 2011). Collagen VII (COL7A1) for example is a functionally important adhesion molecule of the dermal-epidermal junction zone (DEJZ). Epidermal keratinocytes and dermal fibroblasts both synthesise and secrete collagen VII to form anchoring fibrils that attach the epidermis strongly to the dermis. In DEB, the COL7A1 gene is mutated resulting in reduced or absent collagen VII synthesis.

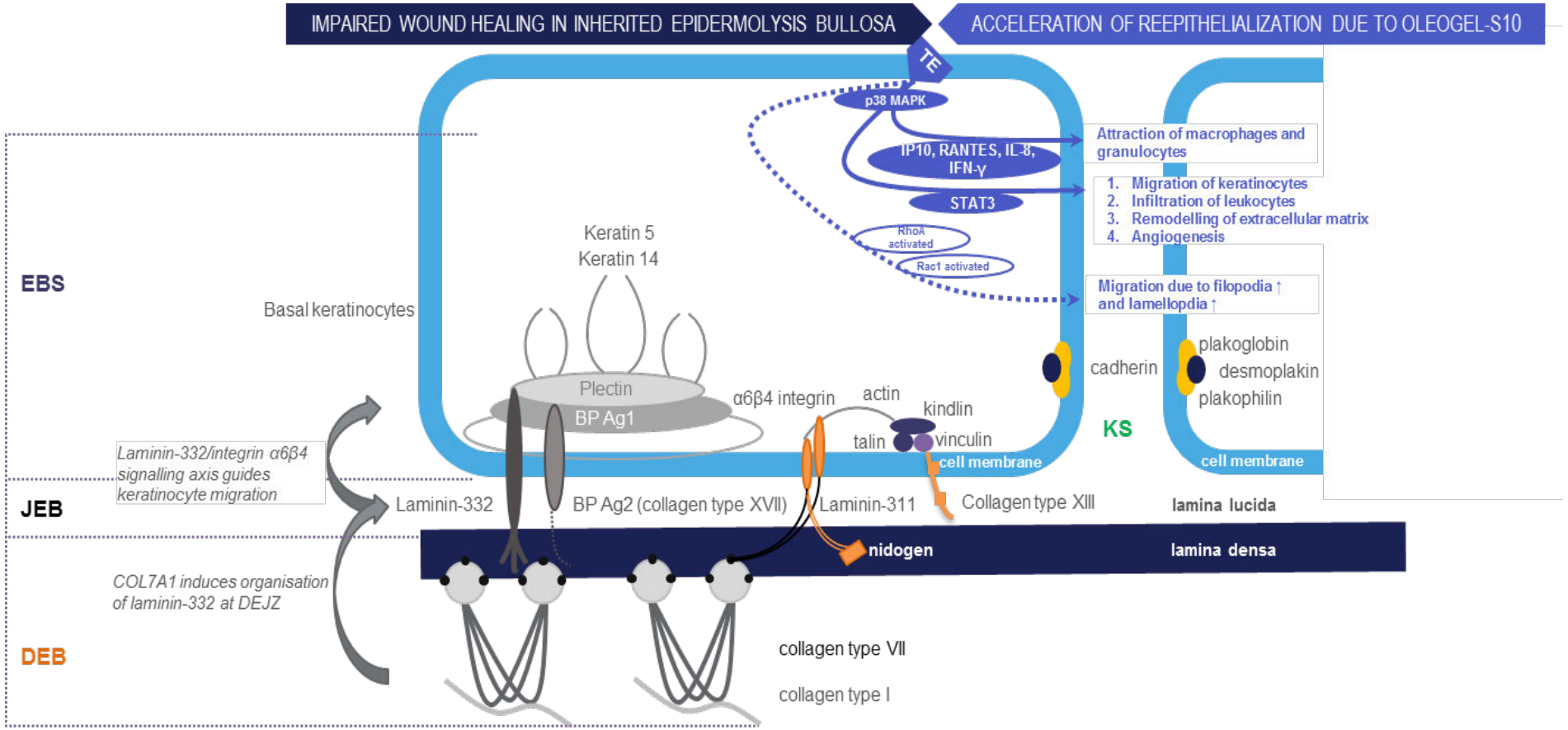
Nystrom et al. investigated the role of COL7A1 in wound healing using 2 different mouse models of genetic skin fragility. They have shown that COL7A1 was a critical player in physiological wound healing based on 2 interconnected mechanisms: First, COL7A1 was required for reepithelialisation through organisation of laminin-332 at the dermal-epidermal junction. The loss of COL7A1 perturbed laminin-332 organisation during wound healing, which in turn abrogated strictly polarised expression of integrin α6β4 in basal keratinocytes and negatively influenced the laminin-332/integrin α6β4 signalling axis guiding keratinocyte migration. Second, COL7A1 supported dermal fibroblast migration and regulated their cytokine production in the granulation tissue. These findings were validated in human wounds (Nystrom, Velati et al. 2013). Since laminin-332 and integrin α6β4 are either absent or markedly reduced in JEB due to mutations of LAMA3, LAMB3, LAMC2, ITGB4, and ITGA6 genes, wound healing could be delayed for the same reason in this disorder. In fact, it has clinically been described that patients with generalised severe JEB heal slowly and it has been suggested that the deficiency of laminin-332 was the reason (Fine 2010, Boeira, Souza et al. 2013).

Oleogel-S10 accelerates the reepithelialisation of wounds, which is thought to be due to an enhancement of keratinocyte proliferation and migration as well as keratinocyte differentiation. Hence, Oleogel-S10 induces different pathways of keratinocyte proliferation,

migration, and differentiation compared with the genetically altered pathways in inherited EB (see Figure 4) (Ebeling, Naumann et al. 2014).

Therefore, different EB subtypes can be assumed to respond equally to treatment, although wound healing may be impaired at different stages. The structural integrity of the skin is compromised at different proteins depending on the EB subtype. However, reepithelialisation and keratinocyte migration, where birch bark extract is thought to be active, are not directly affected by these mutations.

Figure 4 Acceleration of Reepithelialisation due to Oleogel-S10 Versus Impaired Wound Healing in Inherited Epidermolysis Bullosa



Amryt Pharma Figure

BP Ag = bullous pemphigoid antigen; DEB = dystrophic EB; DEJZ= dermo-epidermal junction zone; EB = epidermolysis bullosa; EBS = EB simplex; KS = Kindler Syndrome; IFN-γ = interferon-gamma; IL-8 = interleukin-8; IP-10 = IFN-γ inducible protein 10; JEB = junctional EB; MAPK = mitogen-activated protein kinase; Rac1 = Ras-related C3 botulinum toxin substrate; RANTES = Regulated on Activation, Normal T Cell Expressed and Secreted (chemokine); RhoA = Ras homolog gene family, member A; STAT3 = Signal Transducer and Activator of Transcription 3 (transcription factor); TE = birch bark extract
Source: (Fine, Eady et al. 1999, Boeira, Souza et al. 2013, Ebeling, Naumann et al. 2014)

2.4 Summary of Clinical Studies with Oleogel-S10

2.4.1 Split-Thickness Skin Graft Donor Sites

Two blindly evaluated, randomised, controlled, phase III studies (EudraCT nos. 2012-003390-26 and 2012-000777-23) investigated the intra-individual difference in time to wound closure in STSG donor sites of 219 adult patients.

Donor site wounds were divided into 2 equal halves and were randomised 1:1 to Oleogel-S10 plus non-adhesive wound dressing or to the same non-adhesive wound dressing only, as standard of care (SOC) control (mostly used was Mepilex®). Wounds were treated until complete closure of both wound halves, for a maximum of 28 days. Wound dressings were changed every 3 to 4 days. Oleogel-S10 accelerated wound healing compared with SOC ($p<0.0001$) (Barret, Podmelle et al. 2017).

2.4.2 Grade 2a Burn Wounds

An open, blindly evaluated, prospective, intrapatient controlled, randomised, phase III study (EudraCT No. 2012-000362-38) investigated the efficacy and tolerability of Oleogel-S10 in accelerating the healing of Grade 2a burn wounds. The target wound was divided into 2 halves of similar size; 1 half was treated with Oleogel-S10 and covered with fatty gauze dressing, the other half was treated with Octenilin® Wound Gel and was also covered with fatty gauze dressing, as a SOC control.

Overall, 61 adult patients were enrolled into the study. In blinded assessment of wound photographs, earlier healing was demonstrated for the wound halves that had been treated with Oleogel-S10 compared to those treated with SOC control ($p<0.0001$) (Frew, Rennekamff et al. 2018.

2.4.3 Epidermolysis Bullosa

Case Studies

Oleogel-S10 has been successfully used for the treatment of chronic wounds in a case series of 4 patients with different subtypes of EB: Of those, a 57-year-old male with DEB presented with a chronic wound on the scrotal area present for 3 months. Within 6 days of treatment, the wound size decreased from 9.48 cm^2 to 0.65 cm^2. In a 3-year old girl with JEB, the size of a chronic abdominal wound decreased within 2 days of treatment from 13.63 cm^2 to 9.58 cm^2. A 4-year old boy with EBS had chronic wounds on the upper back and lower abdomen that completely healed within 3 months of treatment with Oleogel-S10.

Open-label, Prospective, Controlled, Blindly Evaluated, Phase II Study

An open-label, prospective, controlled, blindly evaluated, phase II study at the University Medical Centre Freiburg, Germany compared - intra-individually - the efficacy and tolerability of Oleogel-S10, versus non-adhesive wound dressing only, in accelerating the epithelialisation of skin lesions in patients with inherited EB during a treatment period of 28 days.

The primary efficacy variable of the study was the progress of reepithelialisation from baseline to either Day 14 in ‘recent wounds’ or Day 28 in ‘chronic wounds’; with the half of the wound treated with Oleogel-S10 and non-adhesive wound dressing compared to the other half of the wound covered with non-adhesive wound dressing only (intra-individual comparison).

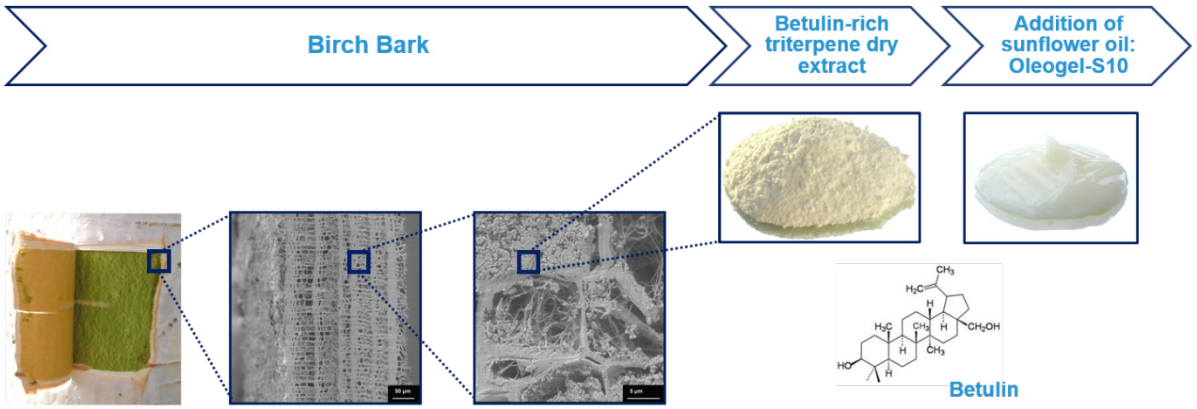
Overall, 10 patients were enrolled into the study; 9 patients had RDEB and 1 patient DDEB localised. As 2 patients received 2 consecutive cycles of treatment, 12 wounds were treated with study medication.

Based on blinded analysis of wound photographs, Oleogel-S10 and non-adhesive wound dressing accelerated the reepithelialisation of wounds in inherited EB compared to non-adhesive wound dressing only (Schwieger-Briel, Kiritsi et al. 2017).

2.5 Rationale for Dose Selection

Oleogel-S10 has a unique composition. The active pharmaceutical ingredient birch bark extract is a white powder consisting of 80% betulin and other closely related triterpene compounds, namely betulinic acid, lupeol, oleanolic acid, and erythrodiol. Triterpenes are able to gel oil, enabling a formulation that consists only of an oil and the active pharmaceutical ingredient without any supplemental ingredients (see Figure 5).

Figure 5 Composition of Oleogel-S10



Amryt Pharma Figure

The active pharmaceutical ingredient concentration of 10% weight per weight provides optimum physical properties of the formulation, being a thick gel that allows for good coverage of the wound. The 10% concentration was used in the clinical development programme in partial thickness wounds, as early clinical studies in other skin conditions showed good safety and tolerability of the formulation with poor systemic absorption.

In all phase II and phase III partial thickness wound studies, Oleogel-S10 has been applied at doses of 100 to 115 mg/cm^2 in wound sizes ≥ 10 cm^2 up to ≥ 40 cm^2 every 1 to 4 days (see Table 1).

Table 1 Doses of Oleogel-S10 in Previous Partial Thickness Wound Studies

Study	Phase	Indication	Dose	Wound Size	Frequency of Treatment
BSH-10	II	STSG DS	115 mg/cm^2	≥ 10 cm^2	Variable (mean 2.3 days)
BEB-10	II	EB	115 mg/cm^2	≥ 10 cm^2	Every 24 to 48 h
BBW-11	III	Burns Grade 2a	100 mg/cm^2	≥ 40 cm^2	At least every 2 days
BSH-12	III	STSG DS	100 mg/cm^2	≥ 15 cm^2	At least every 3 to 4 days
BSG-12	III	STSG DS	100 mg/cm^2	≥ 15 cm^2	At least every 3 to 4 days

EB = Epidermolysis bullosa; STSG DS = Split-thickness skin graft donor site

Patients in this EB Phase III study will be allowed to apply study medication at least every 4 days, since efficacy and safety has been shown in all studies. No cases of Oleogel-S10 overdose have been reported. The maximum exposure achieved in nonclinical studies is 1100 ng/mL. Nonclinical safety and toxicology studies have not demonstrated any dose-limiting toxicities. Since Oleogel-S10 is administered topically, overdose is considered unlikely. Patients in this clinical trial will be closely monitored for any adverse events, and treatment will be terminated if felt appropriate. Based upon the pharmacological properties of Oleogel-S10, no additional specific measures are advised.

There is no standard wound care in EB as described in Section 2.1.3 *Treatment Options and Medical Need*. Wound management in EB depends on several factors including the subtype of the disease, the age of the patient, the current condition of the skin, the availability of wound dressings, an optional involvement of nursing care at home, and the domestic environment (Diem and Sailer 2012).

EB patients usually need to plan their wound dressing changes, because they require external support (e.g., nursing care or relatives), large amounts of wound care products, drugs (anaesthetics or analgesics), a convenient and clear environment, and time.

The study burden will be decreased markedly for patients and caregivers, if patients are allowed to keep their usual schedule of dressing changes.

2.6 Known and Potential Benefits and Risks

Skin blistering with associated recurrent and persistent wounds is the hallmark of most EB subtypes. Self-reported perception of disease severity closely relates to the body surface area affected by EB wounds, the frequency of infected and chronic wounds, and pain (Schwieger-Briel, Chakkittakandiyil et al. 2015). Only 5 to 14% of all paediatric EB patients reported to be pain-free (Fine, Johnson et al. 2004). Itch was present in 87% among children and adults with EB. It increased with increasing number of wounds ($p<0.001$) and was strong in infected wounds ($p=0.002$) (Danial, Adeduntan et al. 2015). Infected and chronic wounds belong to the most frequent complications in the generalised intermediate and severe forms of EB (El Hachem, Zambruno et al. 2014).

The knowledge on wound care in EB is still limited by the paucity of scientific evidence with most recommendations based on expert opinion (Pope, Lara-Corrales et al. 2012). Current treatment of EB is primarily preventive including protection from mechanical forces, early treatment of lesions to prevent superinfections, and protection of the wound with adequate non-adhesive dressings to enable wound healing (Denyer and Pillay 2012, Pope, Lara-Corrales et al. 2012).

The acceleration of wound healing would meet an important medical need, as it would reduce disease burden by decreasing the risk of wound infection and relieving pain and itch.

Oleogel-S10 is authorised in the European Union for treatment of partial thickness wounds in adults under the brand name Episalvan since January 2016 (EU/1/15/1069). It was safe and well tolerated throughout the clinical development programme in partial thickness wounds. The most common adverse events (AEs) related to Oleogel-S10 concerned 25 of 280 patients (9%), comprising pain of skin (2.9%) and pruritus (1.4%). Intensive non-clinical in vitro and in vivo experiments in different species of different ages and different routes of administration up to long-term chronic use raise no concerns for conducting clinical trials. No adverse effects have been observed in single and repeated dose experiments, in safety pharmacology tests, and in the genotoxic evaluation. Oleogel-S10 can be considered as safe when applied to the (abraded) skin based on the results of all toxicological experiments.

Oleogel-S10 has successfully been used for the treatment of EB wounds in 4 patients with different subtypes of EB as well as in a phase II study with 10 patients suffering from RDEB or DDEB. It has been shown to accelerate the reepithelialisation of partial thickness wounds in patients with Grade 2a burns and STSG donor sites.

In conclusion, the benefits of Oleogel-S10 outweigh its risks for an administration in patients with EB.

2.7 Study Rationale

The purpose of this double-blind, randomised, vehicle-controlled, phase III study is to compare the efficacy, safety, and tolerability of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B) in patients with inherited EB (subtypes JEB, DEB, or Kindler syndrome). In

addition, the long-term effect of Oleogel-S10 will be assessed during an open-label, 24-month follow-up (FU).

2.7.1 Rationale of the Study

The proven safety and efficacy of an authorised product in partial thickness wounds on the one hand and the proof of principle as well as the high medical need in EB on the other hand are the rationales for initiating this study.

Oleogel-S10 is authorised in the European Union for the treatment of partial thickness wounds in adults under the brand name Episalvan since January 2016 (EU/1/15/1069).

Oleogel-S10 was safe and well tolerated throughout the clinical development programme in partial thickness wounds. Non-clinical *in vitro* and *in vivo* experiments with Oleogel-S10 have not raised any safety concerns.

Oleogel-S10 accelerated wound healing compared with SOC in STSG donor site wounds, ($p<0.0001$) (see Section 2.4.1 *Split-Thickness Skin Graft Donor Sites*) and in Grade 2a burn wounds ($p<0.0001$) (see Section 2.4.2 *Grade 2a Burn Wounds*).

Oleogel-S10 has been successfully used for the treatment of chronic wounds in a case series of 4 patients with different subtypes of EB and accelerated the reepithelialisation of wounds in inherited EB compared to non-adhesive wound dressing only (see Section 2.4.3 *Epidermolysis Bullosa*).

The acceleration of wound healing would meet an important medical need, as it would reduce pain, itch, and the risk of wound infection (see Section 2.1.3 *Treatment Options and Medical Need*).

2.7.2 Rationale of Study Design

Although skin blistering with associated recurrent and persistent wounds is the hallmark of EB, there are different clinical subtypes presenting with diverse symptoms and variable clinical severity, ranging from mild to debilitating, life-limiting disease. Only few intervention studies have been initiated in EB due to factors well recognised in other orphan diseases such as small number of patients and multiple complications making the patient a less-than-ideal candidate for research studies (Schwieger-Briel, Chakkittakandiyil et al. 2015). EBS patients will not be included in the study. This subtype of EB has the mildest form of the disease with the shortest wound healing cycle times, and hence would be the least likely to derive a substantial treatment benefit. Therefore, inclusion of these patients is likely to dilute the overall treatment effect. Exclusion of these patients will help to ensure that healing rates in the control arm of the study will not be too high and thus avoid a reduction in statistical power while increasing the likelihood of demonstrating a statistically significant treatment effect in other treatment groups.

A vehicle-controlled study allows for a parallel-group design with randomisation and blinding thereby reducing allocation bias and balancing confounding variables.

A 2-arm parallel-group design with vehicle gel control was chosen, because many EB patients apply creams or ointments on those wounds that tend to adhere to wound dressings (Diem and Sailer 2012). The use of topical emollients including moisturisers for skin care is widely recommended for EB patients (Denyer and Pillay 2012, El Hachem, Zambruno et al. 2014). Equal parts of liquid paraffin and white soft paraffin are also used for (periwound) skin care (Denyer and Pillay 2012). Overall, greasy ointments (e.g., Vaseline®) are used most frequently, particularly for the management of pruritus (Danial, Adeduntan et al. 2014). The use of a sunflower oil gel as vehicle control provides patients in the control arm also with such a greasy ointment. As no well-defined SOC cream or ointment exists, the use of this vehicle control will not only provide a standard SOC for EB treatment, but also a comparison of vehicle versus Oleogel-S10 (both share sunflower oil as the main ingredient) and a control group suited for a double-blind study design.

2.7.3 Rationale of Primary Efficacy Endpoint – Double-blind Phase

The primary efficacy endpoint of the double-blind phase (DBP) will be the 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 (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 will be rated as "closed" at first appearance of complete reepithelialisation without drainage.

There are no published data on either the natural history of the disease process in EB or the expected response to SOC. Therefore, an EB partial thickness wound aged ≥ 21 days is considered to be delayed in wound healing. Partial thickness wounds normally heal within 1 to 3 weeks (Doughty 2012). In burn victims, partial thickness wound aged ≥ 21 days are covered with STSGs to avoid complications of delayed wound healing such as scarring.

There is no guidance on the specified time of an '*acute*' EB wound becoming '*chronic*', although the consensus meetings on the development of the '*Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa*' (iscorEB) defined wounds in EB to be chronic, if they are present for longer than 6 weeks (Schwieger-Briel, Chakkittakandiyil et al. 2015). Younger and particularly smaller wounds <10 cm^2 are more dynamic and tend to heal on their own. In chronic wounds, multiple factors such as nutritional deficiencies, an infection, or repeated trauma contribute to the delay of healing.

Oleogel-S10 accelerates the reepithelialisation of wounds due to an enhancement of keratinocyte differentiation and migration. Hence, its mechanism of action would target those wounds that are delayed in wound healing being prone to become a chronic wound. These wounds are of high clinical relevance and a major source of complications in patients with EB.

The assessment for the primary endpoint follows the US Food and Drug Administration (FDA) Guidance for Industry '*Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment*'.

2.7.4 Rationale of Secondary Efficacy Endpoints – Double-blind Phase

One of the key secondary (confirmatory) efficacy endpoints of the DBP will be 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 (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 JEB, DEB, or Kindler syndrome) in either treatment arm as evidenced by clinical assessment until D90±7. The time taken to achieve complete wound healing is a clinically important endpoint for the assessment of the potential benefit of a wound healing treatment in EB. More rapid wound healing results in fewer symptoms related to open wounds (e.g., pain and itching), and would be expected to decrease the likelihood of wound infection.

The assessment for this key secondary (confirmatory) endpoint follows the US FDA Guidance for Industry '*Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment*'.

Further secondary efficacy endpoints of the DBP will include: time to first complete closure of the EB target wound as evidenced by blinded evaluation of photographs taken until D90±7; proportion of patients with first complete closure of the EB target wound within D14±5, D30±7, D60±7 and D90±7 based on clinical assessment by the investigator; and proportion of patients with 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.

In addition, further secondary efficacy endpoints have been determined to demonstrate the impact of accelerated healing such as the difference in EB target wound size reduction, the

change in total body wound burden, the change in percentage of TBSA affected by EB partial thickness wounds, the difference in wound infection rates, the change in impact of wounds on sleep, the change in "background" and "procedural" pain, the change in itch, and the evaluation of the response to treatment.

2.7.5 Rationale of Endpoints – Open-label Follow-up Phase

The primary rationale of the open-label FU phase is to obtain long-term safety data and real-world data on severity and quality of life; apart from that the rationales of the other assessments in particular at the first visit at Month 3 (M3)±14 days are comparable to those in the DBP.

3 STUDY OBJECTIVES

3.1 Primary Objective – Double-blind Phase

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 EB partial thickness wounds. This will be 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 JEB, DEB, or Kindler syndrome) within 45±7 days of treatment.

3.2 Secondary Objectives – Double-blind Phase

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 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 AEs, and based on laboratory assessments
- Compare the tolerability of Oleogel-S10 (treatment arm A) with vehicle (treatment arm B)

- Assess betulin exposure

3.3 Objectives – Open-label Follow-up Phase

The objectives of the 24-month, open-label FU phase are to:

- 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 first complete closure of the EB target wound at M3±14 days
- Assess the changes from baseline of both DBP (Day [D] 0) and FU (D0)/end of DBP (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 FU (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 FU (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 FU (D0)/EDBP (D90±7) in itch before wound dressing changes at M3±14 days
- Assess the changes from baseline of both DBP (D0) and FU (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 FU (D0)/EDBP (D90±7) in treatment response (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

4 INVESTIGATIONAL PLAN

All references to "the investigator" throughout this document refer to "the investigator or a delegated sub-investigator".

4.1 Study Endpoints

4.1.1 Primary Efficacy Endpoint – Double-blind Phase

The primary efficacy endpoint of the DBP is:

- 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 (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 will be rated as "closed" at first appearance of complete reepithelialisation without drainage)

4.1.2 Secondary Endpoints – Double-blind Phase

The key secondary (confirmatory) efficacy endpoints are:

- Time to first complete closure of the EB target wound as evidenced by clinical assessment until EDBP (D90±7)
- Proportion of patients with first complete closure of the EB target wound at D90±7 based on clinical assessment by the investigator
- 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)
- 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)
- 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
- 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:

- 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
- 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
- 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
- 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
- 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 D30±7 and D60±7
- 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
- Change from baseline (DBP D0) in "background" pain using the '*Face, Legs, Activity, Cry, Consolability*' (FLACC) pain rating 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
- 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

- 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
- 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)
- 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
- 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).

The safety endpoints of the DBP are:

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Systemic exposure to betulin

4.1.3 Endpoints of Open-label Follow-up Phase

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Safety laboratory data
- Systemic exposure to betulin
- Proportion of patients with first complete closure of the EB target wound at M3±14 days based on clinical assessment by the investigator and blinded evaluation of photographs
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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, M12±14 days, and at End of Follow-up (EoFU) at M24±14 days
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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, M12±14 days, and at EoFU at M24±14 days
- Changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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 baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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 baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) 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 baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in impact of wounds on sleep (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 response (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 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 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

4.2 Overall Study Design

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). At the EDBP (Visit 7a on D90±7), patients in both treatment arms will enter the single-arm, open-label FU phase with Oleogel-S10. Each patient will participate for 90±7 days in the randomised DBP. Each patient in the open-label FU phase will receive Oleogel-S10 treatment for 24 months. The total study duration (DBP and open-label FU phase) will be approximately 27 months.

4.2.1 Double-blind Phase

The randomised DBP will consist of 3 periods (see Figure 6):

1. Screening (up to 28 days prior to baseline)

   Study sites contact and invite patients registered in centre-specific databases. Patients who fail screening may be rescreened if he/she later becomes eligible, as deemed appropriate by the investigator.

2. Baseline, enrolment, and stratified randomisation (D0)

   The investigator will confirm eligibility for the patient on D0 corresponding to the study flow chart, check the eligibility criteria, and enrol the patient into the study. The EB target wound will be selected based on the '*Investigator's Worksheet*' displayed in Figure 23. Patients will be stratified according to their EB subtype and target wound size (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 will then be randomised 1:1 to receive either Oleogel-S10 (treatment arm A) or vehicle (treatment arm B) (see Section 9.1 *Baseline, Enrolment, and Stratified Randomisation [D0])*.

3. Intervention (90 days±7 days)

   The treatment of the EB partial thickness target wound and all areas on a patient's body that are affected by EB partial thickness wounds with Oleogel-S10 and SOC non-adhesive wound dressing (treatment arm A) or with vehicle and SOC non-adhesive wound dressing (treatment arm B) as described in Section 7.1 *Treatment Schedule* will start the same day (D0).

Each patient will participate for 90±7 days in the DBP of the study.

4.2.2 Open-label Follow-up Phase

Once the EDBP visit for the randomised DBP has been completed and the return of the corresponding unused study medication has occurred, the patient will enter the single-arm, open-label, 24-month FU phase. The EDBP visit at D90±7 (Visit 7a) corresponds to the first visit (D0) of the FU phase (Visit 7b). The data of total body wound burden and BSAP assessment at EDBP (D90±7) will be used as baseline data of D0 of the FU (see Section 9.5 *Open-label Follow-up Phase*).

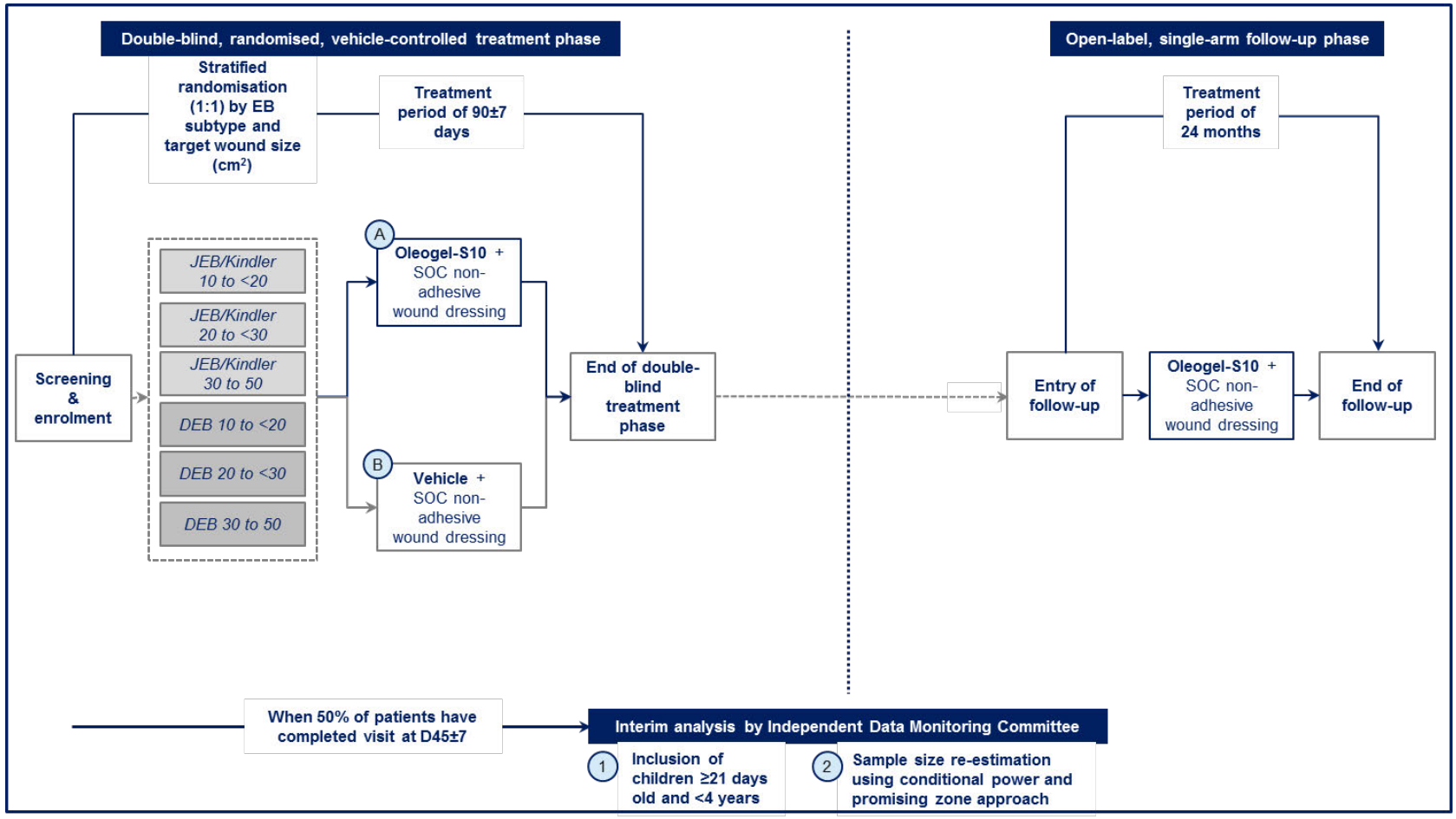
All patients will start with topical Oleogel-S10 administration on D0 of the FU phase to all areas on the patient's body that are affected by EB partial thickness wounds as described in Section 7.1 *Treatment Schedule*. Wound areas will be covered with SOC non-adhesive wound dressings. This procedure will be repeated during all dressing changes based on the study flow chart (at least every 4 days) until the end of treatment at M24±14 days. The investigator may implement a dose interruption if considered medically necessary for optimal management of the patient.

Patients who participate in the FU phase will receive Oleogel-S10 treatment for 24 months. After the EoFU visit, it is intended that patients will receive Oleogel-S10 on a named-patient basis, where feasible as per local regulation, until approval of the investigational product.

4.2.3 End of Trial

The End of Trial is defined as completion of the last visit or assessment for the last subject.

Figure 6 Design of Double-blind, Randomised Treatment Phase and Open-label Follow-up Phase



Amryt Pharma Figure

DEB = Dystrophic EB; EB = Epidermolysis bullosa; JEB = Junctional EB; SOC = Standard of care

5 STUDY POPULATION

5.1 Inclusion Criteria

A patient will be eligible for study participation only if all of the following criteria apply:

1. Male and female patients aged ≥ 4 years with the following subtypes of inherited EB: JEB, DEB, and Kindler syndrome
   Note: Children ≥ 21 days old and <4 years may be included only after confirmation by the Independent Data Monitoring Committee (IDMC) upon review of the safety and bioanalytical data at the interim safety review stage
2. Patients with an EB target wound (i.e., EB partial thickness wound of 10 cm^2 to 50 cm^2 in size, aged ≥ 21 days and <9 months) outside of the anogenital region)
3. Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed consent
4. Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions

5.2 Exclusion Criteria

A patient will not be eligible to participate in this study if any of the following criteria apply:

1. Patient has EB subtype EBS
2. EB target wound that is ≥ 9 months old or has clinical signs of local infection
3. Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment
4. Administration of systemic or topical steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL]) within 30 days before enrolment
5. Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment
6. Patient has undergone stem cell transplant or gene therapy for the treatment of inherited EB
7. Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas
8. Enrolment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry
9. Factors present in the patient and/or his/her legal representative that could interfere with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes
10. Pregnant or nursing women
11. Women of childbearing potential, including postmenarchal female adolescents, and men who are not willing to use an effective form of birth control with failure rates <1% per year (e.g., implant, injectable, combined oral contraceptive, intrauterine contraceptive device, sexual abstinence, vasectomy or vasectomised partner) during participation in the study (and at least 3 months thereafter)
12. Patient is a member of the investigational team or his/her immediate family
13. Patient lives in the same household as a study participant

6 STUDY MEDICATION

6.1 Description of the Investigational Product

6.1.1 Formulation, Packaging, and Labelling

The investigational product, Oleogel-S10, is a colourless to slightly yellowish, opalescent gel packed in white collapsible aluminium tubes containing 23.4 g gel each. Tamper-evident aluminium membranes close the tubes, which are fitted with white polypropylene screw caps. The single-use tubes are packed in cardboard boxes. The investigational product will be packed and labelled according to applicable regulatory requirements.

Please refer to Section 2.2 *Investigational Product* for the composition of Oleogel-S10.

6.1.2 Storage and Stability

Oleogel-S10 gel is stable for 24 months if stored below 30°C (refer to '*Investigational Medicinal Product Manual*' for more details).

6.1.3 Drug Accountability

A sufficient number of single-use Oleogel-S10 or vehicle tubes will be provided to sites at appropriate intervals depending on the phase of the study and accrual of patients. The investigator, or the person designated by the investigator, will be responsible for dispensing study medication to the patients. The site may ship study medication to a patient's home using a courier if permitted by local regulations.

At each site, the investigator, or the person designated by the investigator, will be responsible for keeping accurate records of study medication accountability comprising the receipt of study medication, the dispensing of study medication, and the return of all used and unused study medication throughout the study. The drug accountability form should be kept up to date and will be reviewed periodically by the study monitor.

Patients will be asked to keep all used and unused tubes and return them to the site during the scheduled visits. For drug accountability, the number of used and unused tubes will be counted and used kits will be weighed. The data on frequency of dressing changes during the study will be used to support drug accountability. All unused tubes will be redispensed to the patient after drug accountability is completed by the site study team member.

For estimations of drug compliance, treatment interruptions will be recorded on the electronic Case Report Form (eCRF) and compliance will be calculated as (treatment end date – treatment start date +1 – treatment interruptions in days) / (treatment end date – treatment start date +1). The compliance calculation will be adjusted for variations in drug application due to changes in wounds and difference in frequencies of dressing changes.

6.2 Description of the Vehicle

For clarification, please note that the term "vehicle" describes the control/placebo throughout this protocol.

The sterile vehicle gel matches Oleogel-S10 in texture and visual appearance. 100 g of the vehicle gel will consist of 85 g sunflower oil, 5 g Cera flava/yellow wax, and 10 g Carnauba wax.

6.3 Standard of Care Non-adhesive Wound Dressings

Standard of care non-adhesive wound dressings are defined as modern non-adhesive wound dressings or equivalents. Please refer to the 'International Consensus Best Practice

Guidelines for Skin and Wound Care in Epidermolysis Bullosa' for recommended wound dressings in different subtypes and wounds of EB (Denyer and Pillay 2012).

Standard of care varies across geographic regions and between sites. In addition, patients have individual preferences strongly rooted in their personal experience. Therefore, it will probably not be feasible to standardise wound care completely in this study. Hence, patients will be allowed to continue using their SOC non-adhesive wound dressings except for silver dressings and dressings containing topical emollients (e.g. vaselinized gauze). However, it is recommended to reduce the diversity of wound dressings as much as possible, e.g., by using a small number of products, such as Mepitel® (Mölnlycke Health Care AB, Sweden) or PolyMem® (Ferris Mfg. Corp., USA) only.

7 STUDY TREATMENT

7.1 Treatment Schedule

The investigator will explain to the patient and/or to his/her legal representative that the wound dressings will have to be changed and the study medication will have to be applied at least every 4 days. The patient can keep his/her usual schedule of wound dressing changes; for example every day, every second, third, or fourth day as long as he/she does not wait longer than 4 days until the next wound dressing change. The patient will be asked to keep a regular schedule of wound dressing changes (i.e., not to change intervals between wound dressing changes) and to report this schedule to the investigator.

The patient will be allowed to apply the study medication directly to the wound or to the area of the wound dressing that will be used to cover the wound so that the study medication is in direct contact with the wound, based on personal preference.

Both the EB target wound and all areas on the patient's body that are affected by EB partial thickness wounds will be treated with study medication. The study medication should not be rubbed into the wounds. The study medication should not be mixed with other skin products such as creams, ointments, gels, or emollients, or applied with such skin products at the same time. 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 to the closed wound. The patient may dress the wound to protect the area, if required.

Products and dressings that are permitted or not permitted for use in conjunction with the study medication during the DBP and the open-label FU are described in Section 7.5.1 *Permitted Concomitant Medication* and Section 7.5.2 *Non-permitted Concomitant Medication*.

Areas on the patient's body that are not affected by EB partial thickness wounds are not to be treated with study medication. The study medication is not intended for use on full thickness wounds in this study.
The study medication (Oleogel-S10 or vehicle gel) will be administered topically at approximately 1 mm (0.04 inch) thickness to the EB target wound and to all areas on the patient's body that are affected by EB partial thickness wounds. Wound areas will then be covered with an SOC non-adhesive wound dressing. Alternatively, the study medication may be applied to the dressing first and the medication-covered dressing then placed on the wound so that the study medication is in direct contact with the wound. This procedure will be repeated during all dressing changes based on the study flow chart (at least every 4 days) until EDBP (D90±7).

The open-label treatment with Oleogel-S10 during the FU phase corresponds to the treatment described for the DBP of the study, but lasts until the end of treatment at M24±14 days.

7.1.1 Treatment Assignment/Blinding Procedure

Patients will be 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 will then be randomised 1:1 to receive either Oleogel-S10 (treatment arm A) or vehicle gel (treatment arm B). Investigators and patients both will be blinded for treatment allocation.

Once a randomisation number has been assigned, that number must not be used again for any other patient (e.g., when the patient is withdrawn from the study, that patient's randomisation number must not be reused for any other patient).

An independent unblinded biostatistics team in a separate location will maintain the randomisation scheme key and will only distribute this to approved personnel. This key will remain unavailable to all other individuals until after DBP completion and subsequent locking of the study database for the DBP.

For the purpose of the interim analysis for sample size re-estimation and the unblinded interim safety review to confirm if the study can be expanded to allow the inclusion of children with EB to all ages (i.e., ≥ 21 days and <4 years), the independent unblinded biostatistics team will provide the unblinded results to the approved IDMC members.

During the FU phase, all patients will be treated with Oleogel-S10. Both the investigator and the patient will know the treatment.

7.2 Dose Interruption/Dose Modification for Adverse Events

No treatment-limiting toxicities have been reported in studies of Oleogel-S10 across several indications, including EB; therefore, dose interruptions due to toxicity are not expected. The investigator may implement a dose interruption if considered medically necessary for optimal management of the patient. Dose interruptions are not allowed for using non-permitted concomitant medication (see Section 7.5.2) to treat worsening of wound status, increase in wound size, and wound infections of EB target wounds and other wounds matching target wound criteria (see Section 8.1.2). For worsening of the EB target wound status or EB target wound infections the patient may discontinue the DBP and enter the FU phase prematurely (see Section 7.3). Should any other interruptions of treatment occur, the investigator should be contacted immediately.

7.2.1 Emergency Procedure for Unblinding

Patients should not be unblinded except in an emergency when it is necessary to know the treatment assignment. For example, unblinding may be indicated if:

- There is a medical emergency in a study patient where knowledge of the blinded treatment is necessary to make medical decisions
- There is need to know the treatment assignment in order to treat an AE
- There is a situation in which a child in a patient's household accidentally ingests the study medication
- In the event of a suspected unexpected serious adverse reaction (SUSAR) needing expedited reporting (following the study safety plan)
- Request by the external IDMC

Unblinding is performed in the electronic system iMedidata Balance. This system records the date and time and reason for unblinding, as well as the person requesting the code break. The system also notifies the sponsor in a blinded fashion of a code break. Patients who are unblinded by the investigator will not remain in the study.

There will be an unblinded interim analysis for the purpose of a sample size re-estimation performed by the Unblinded Biostatistician and evaluated by the IDMC. Details of the unblinded sample size re-estimation will be described in the Statistical Analysis Plan (SAP). The sample size re-estimation will be performed when approximately 50% of patients have completed D45±7. The final unblinding of the study will not take place until all patients have completed the study, all queries have been resolved, and the database is locked.

7.3 Patient Discontinuation Criteria

Patients and/or his/her legal representatives will have the right to withdraw from the study at any time for any reason without prejudice to their future medical care.

The investigator will also be able to withdraw patients from the study for the following reasons:

- Worsening of the EB target wound status or EB target wound infection as assessed by the investigator
- Patient is non-compliant with the study procedures or medications in the opinion of the investigator
- Progression of a medical condition, which in the opinion of the investigator should preclude further participation of the patient in the study
- Administration of non-permitted concomitant medication(s)
- Investigator's decision that a change of therapy is in the patient's best interest
- Occurrence of an AE, which makes discontinuation desirable or necessary in the investigator's and/or the patient's opinion

  If a patient discontinues the DBP or the FU phase prematurely due to an AE/serious AE (SAE), every effort will be made to follow the patient until the resolution of the AE/SAE. If a patient discontinues the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection, the investigator may decide whether the patient enters the FU phase prematurely or discontinues the study completely.
- Pregnancy as evidenced by a positive pregnancy test

  If a patient or the partner of a male patient becomes pregnant during the study, during the FU phase, or 30 days within the last application of study medication, the sponsor must be informed within 24 hours. The investigator will be asked to complete a pregnancy report provided by the sponsor. The investigator will be asked to obtain data on the course of the pregnancy, including perinatal and neonatal outcome up to 28 days after delivery (see Section 11.4.2 *Other Reportable Information*).

If a patient discontinues the study prematurely during the DBP, the EDBP (D90±7) visit assessment should be performed (see Section 9.4 *Visit 7a [Site Visit at D90±7] End of Double-blind Phase*). In case the patient discontinues the FU phase prematurely, the assessments scheduled for the EoFU visit should be performed (see Section 9.5.5 *End of Follow-up Visit 10 [M24±14 Days]*).

All data collected before premature discontinuation of the study will be used for analysis. Patients who drop out will not be replaced.

7.4 Overdose

No cases of Oleogel-S10 overdose have been reported. The maximum exposure achieved in nonclinical studies is 1100 ng/mL. Nonclinical safety and toxicology studies have not demonstrated any dose-limiting toxicities. Since Oleogel-S10 is administered topically, overdose is considered unlikely. Patients in this clinical trial will be closely monitored for any adverse events, and treatment will be terminated if felt appropriate. Based upon the

pharmacological properties of Oleogel-S10, no additional specific measures are advised. Standard medical care should be used to monitor patients with an assumed or documented overdose with Oleogel-S10.

7.5 Concomitant Medication

7.5.1 Permitted Concomitant Medication

The following medication will be permitted during both phases of the study (DBP and open-label FU phase):

- Liquid antiseptics such as polyhexanide, iodine products, or octenidine dihydrochloride at each wound dressing change to clean the EB target wound (and other wounds matching target wound criteria) and/or to reduce microbial colonisation of the EB target wound (and other wounds matching target wound criteria) prior to study treatment
- Bathing (e.g., with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change (Denyer and Pillay 2012)
- Systemic antibiotics except for treatment of EB target wound (and other wounds matching target wound criteria) infections
- Inhaled, ophthalmic, or topical steroids, such as budesonide suspension for oesophageal strictures (e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL)
- Supportive therapy upon the investigator's discretion

On single EB wounds (except for the EB target wound and other wounds matching target wound criteria), the following medication will be permitted during both the DBP and FU phase of the study:

- Silver sulfadiazine
- Topical antibiotics
- Topical steroids

7.5.2 Non-permitted Concomitant Medication

The following medication will not be permitted during the study until M3±14 days of the open-label FU:

- Systemic steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules® 0.25 mg/2 mL or 0.5 mg/2 mL])
- Immunosuppressive therapy or cytotoxic chemotherapy
- Systemic antibiotics to treat EB target wound (and other wounds matching target wound criteria) infections

On areas on the patient's body that are affected by EB wounds, the following medication will not be permitted during the DBP of the study:

- Skin products such as creams (including barrier creams), ointments (and dressings containing topical emollients e.g. vaselinized gauze), gels, or emollients

On the EB target wound (and other wounds matching target wound criteria), the following medication will not be permitted until complete closure and confirmed epithelialisation during both the DBP and FU phase of the study:

- Silver dressings
- Silver sulfadiazine

- Topical antibiotics
- Topical steroids

8 ASSESSMENTS

Please refer to Section 1.2 *Flow Chart of Study (Randomised, Double-blind and Open-label Follow-up)* for a tabular overview of assessments by visit.

8.1 Eligibility and Safety Assessments

8.1.1 Eligibility Assessments

Informed Consent

The investigator will obtain written informed consent from the patient and/or his/her legal representative(s) before he/she will initiate any study-specific procedure. For this study in patients <18 years, in addition to information sheets and consent/assent forms for patients (according to applicable local regulations), parent/legal guardian information sheets and consent forms will also be prepared.

The following criteria will be assessed for eligibility prior to enrolment:

Inclusion/Exclusion

The investigator will assess the patient's eligibility as outlined in Section 5.1 *Inclusion Criteria* and Section 5.2 *Exclusion Criteria* including confirmation of a negative urine pregnancy test in women of childbearing potential and postmenarchal female adolescents.

Demographics

Age, gender, ethnic origin, Fitzpatrick skin type (Fitzpatrick 1988), height, and weight will be recorded at baseline.

Medical History/Current Medical Conditions

The investigator will ask the patient and/or his/her legal representative(s) for the patient's general and disease-specific medical history and current medical conditions. The investigator will record the EB subtype as well as the date and method of diagnosis (e.g., genetic analysis, immunofluorescence mapping, transmission electron microscopy). If genetic confirmation of EB subtype is not available for the patient, the patient will be asked to consent to additional testing for genetic confirmation of EB subtype. Consent to the additional genetic testing is optional, and written informed consent can be given at any visit during the study.

Physical Examination

The investigator will do a complete physical examination of the patient and will document all clinically relevant findings including systemic manifestations of EB.

Selection of Target Wound

The investigator will select 1 EB target wound based on the '*Investigator's Worksheet*' displayed in Figure 23. Target wounds must be EB partial thickness wounds of 10 cm^2 to 50 cm^2 in size and must be aged ≥ 21 days and < 9 months. Wounds in the anogenital region should not be chosen as target wounds, however, wounds close to this region may be selected provided it is possible to apply dressings in accordance with Section 7.1 and there are no privacy concerns regarding these wounds.

In the event of several EB partial thickness wounds match the target wound criteria, the wound of the largest size, maximum depth and longest duration should be chosen as the target wound, based on the investigator's clinical judgement. The target wound and all other wounds that match target wound criteria must be mapped for size, location and duration in a

body chart and appropriately photo-documented until complete closure or until M3±14 days of the open-label FU phase. Information regarding size and location of all wounds that match the target wound criteria will be captured in the database.

8.1.2 Safety Assessments

Concomitant Medication

During the DBP and open-label FU phase, all concomitant medications will be recorded.

Adverse Events

Adverse events occurring before the first administration of study medication will be recorded in the Medical History/Current Medical Conditions section of the eCRF. AEs occurring during the treatment period of the DBP and the FU phase until 4 weeks after the last administration of study medication (Oleogel-S10 or vehicle) will be recorded in the AE section of the eCRF. During the screening period (<D0) and at baseline (D0 of the DBP) before study medication administration, AEs related to study procedures should also be reported. For reporting of AEs, please refer to Section 11.2 *Recording of Adverse Events and Serious Adverse Events*.

Worsening of wound status, increase in wound size, re-opening of wounds and wound infections should be reported as AEs. Assessment of wound status and wound size should be in comparison to baseline (DBP) and not the previous visit. It should be ensured that clinical signs are present for wound infections, i.e., mere colonisation of the wound with proliferating bacteria without a host response is not to be reported as AE.

Serious Adverse Events

Serious AEs will be recorded in the SAE section of the eCRF during screening, at baseline, during the DBP, and the 24-month, open-label FU phase. For reporting of SAEs, please refer to Section 11.4 *Immediately Reportable Information*.

Local Tolerability

Local tolerability will be judged by the investigator continuously throughout the study.

Vital Signs

Vital signs (heart rate, respiratory rate, and body temperature) will be recorded at baseline, at D90±7 of the DBP, and at M24±14 days of the open-label FU.

Electrocardiogram

An electrocardiogram (ECG) will be performed at baseline, at D90±7, and at M24±14 days, where available. The ECG recordings are to be 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”. The reason(s) for ‘abnormal’ findings should be documented. 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).

Laboratory Assessments

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]); and betulin levels. Laboratory safety assessments samples are to be taken at baseline, at D90±7, 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. The volume of blood taken for blood draws should follow local protocols for

safe blood sampling by age group, i.e. smaller volumes should be taken in younger children according to the local laboratory policy.

Blood tests for Betulin Analysis

As well as the mandatory safety laboratory samples, patients will be asked to provide written informed consent for collecting additional optional blood samples up to M24±14 days of the open-label FU. Betulin levels will be analysed in dried blood spots that will be sent to the central laboratory (Nuvisan GmbH, Germany).

Pregnancy Tests

Urine pregnancy tests will be conducted in women of childbearing potential/postmenarchal female adolescent patients using test strips provided by Amryt Research Ltd. at DBP baseline (D0) and EDBP (D90±7), and M3±14 days, M12±14 days, and M24±14 days of the open-label FU. If a pregnancy test has been performed within 14 days prior to baseline it does not need to be repeated at baseline.

8.2 Assessment of Efficacy

A training programme will be provided to site study team members for all efficacy assessments.

Assessment of wound status should be in comparison to baseline (DBP) and not the previous visit.

8.2.1 Photography of EB Target Wound and Other Wounds

The investigator or delegated site study team member will photo-document the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system for blinded efficacy assessment by 3 independent experts.

The Silhouette® system consists of the SilhouetteStar™ point of care imaging device (see Figure 7 a) that captures the wound image using 3-D laser technology (see Figure 7 b). In addition, it provides the SilhouetteConnect™ software, which creates a 3-D model of the wound based on photo-data, derives measurements of the model, and records standardised notes (see Figure 7 c).

Figure 7 Target Wound Photography with the ARANZ Silhouette® System

Source: ARANZ Medical Ltd., Christchurch 8140, New Zealand

The ARANZ Silhouette® system measures accurately, precisely, and reliably, provides high quality imaging, and a standardised documentation. The Silhouette® system is compliant with all major accreditation marks. Regulatory clearance includes an FDA Class 1 approval (US) along with CE Mark (Europe), Health Canada – Therapeutic Products Directorate (Canada), and Therapeutic Goods Administration approval (Australia).

The investigator and authorised site study team members will receive both the ARANZ Silhouette® system and a standardised training before start of the study. The '*Photo*

Documentation Manual' will provide a detailed description of the ARANZ Silhouette® system, instructions for use, and a standard operating procedure of target wound photography.

During screening, the investigator will select the EB target wound as described in the '*Investigator's Worksheet*' (see Figure 23). Before start of treatment, he/she will select 2 appropriate anatomical landmarks on either side of the EB target wound. He/she will document the landmarks used. The investigator or delegated site study team member will take a baseline reference image with these landmarks. He/she will create a separate image of the EB target wound with tracings. At future visits, the investigator or delegated site study team member will always refer to the baseline reference image to ensure that the correct wound is assessed. All other wounds that match target wound criteria will be photo-documented similarly.

The baseline reference image(s) of the target wound and of other wounds that match target wound criteria will be uploaded to the wound documentation report and the results will be recorded in the eCRF as described in the '*Photo Documentation Manual*'. Photo compilations by visit will be prepared for the blinded expert landmark analysis (i.e., presence of complete wound closure and EB target wound size). Details on the blinded expert assessments of the target wound and of other wounds that match the target wound criteria will be determined in a separate plan and results analysed per the SAP.

8.2.2 Total Body Wound Burden

An investigator will assess the change in total body wound burden clinically using Section I (assessment of the skin except for the anogenital region) of the EBDASI (see Figure 8) (Loh, Kim et al. 2014).

The EBDASI is a reliable and valid instrument for inherited EB of all ages and subtypes, which scores activity response to therapy separately from damage. It consists of 5 sections, namely Section I '*Skin*', Section II '*Scalp*', Section III '*Mucous Membranes*', Section IV '*Nail Disease*', and Section V '*Other Surfaces and SCC [squamous cell carcinoma]*'. Since this study will investigate medication for cutaneous use, Section I will be used only.

8.2.3 Body Surface Area Percentage

An investigator will assess the change in BSAP of TBSA affected by EB partial thickness wounds clinically using a matrix based on the '*Lund and Browder*' chart (see Figure 9) (Miminas 2007).

There are 3 approaches to assess BSAP, the '*Rule of Nines*', the '*Rule of Palms*', and the '*Lund and Browder*' chart. The '*Lund and Browder*' chart is regarded as the most accurate and is widely used in the management of burn patients. It consists of 2 drawings of the anterior and posterior part of the human body. The BSAP of the respective regions appear either on the drawings or on a corresponding table providing the BSAP by age. The matrix that has been prepared for the evaluation of the change in BSAP affected by EB partial thickness wounds in this study is based on these regional weighing factors by age to account for the different proportions of children to be included in this study.

While Section I of the EBDASI measures the total body wound burden consisting of erosions, blisters, and crusting, the matrix based on the '*Lund and Browder*' chart measures the BSAP of EB partial thickness wounds only.

8.3 Patient-reported Outcomes

Amryt Research Ltd. evaluated Patient-reported Outcome (PRO) instruments based on the target patient population, the clinical study objectives and design, the PRO instrument's conceptual framework, and the PRO instrument's measurement properties as recommended in the 2009 FDA guidance for *industry 'Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims'*. Since a Health-related Quality of Life

instrument evaluating age-appropriate concepts for EB was not available and content validity was lacking in the majority of Health-related Quality of Life measures (Mordin, Clark et al. 2012), the concepts 'pain', 'itch', 'impact of wounds on sleep', and the patient's satisfaction with treatment will be assessed with concept-specific PRO instruments instead.

Standardised training for PROs will be provided to ensure consistent instructions are given to patients, and to provide sites with standardised guidance in reviewing data and answering questions about the scales. If a legal representative completes the assessments, the investigator should make sure, that preferably the same legal representative completes the assessments each time to limit variability.

8.3.1 'Itch Man Scale'

In patients ≥ 4 years and up to 13 years of age, itching will be assessed using the '*Itch Man Scale'* (see Figure 10) (Morris, Murphy et al. 2012). The '*Itch Man Scale*' is the only measure that specifically assesses itching in children. Blakeney and Marvin developed it in 2000 based on a child's drawing showing his distress with itching. The '*Itch Man Scale'* is a validated itch assessment tool.

8.3.2 'Leuven Itch Scale'

In patients ≥ 14 years of age, itch will be evaluated using the '*Leuven Itch Scale*' (see Figure 11) (Haest, Casaer et al. 2011). The *'Leuven Itch Scale'* is an instrument measuring all dimensions of the itch experience including symptom occurrence (frequency, duration, severity, and circumstances), symptom distress, symptom management, symptom location, sensory perception of the symptom, and consequences of the symptom. Snauwaert et al demonstrated that the *'Leuven Itch Scale'* was an appropriate instrument to measure itch in EB (Snauwaert, Yuen et al. 2014).

8.3.3 'Face, Legs, Activity, Cry, Consolability' Pain Rating Scale

In patients <4 years of age, the investigator or delegated site study team member will use the FLACC scale for assessing "background" pain before wound dressing change and "procedural" pain after wound dressing change (see Figure 12) (Merkel, Voepel-Lewis et al. 1997).

The FLACC pain rating scale is a valid and reliable tool for quantifying pain behaviours in children who may not be able to verbalise the presence or severity of pain. It was found to have high interrater reliability.

8.3.4 'Wong-Baker FACES Pain Rating Scale'

In patients ≥ 4 years of age, '*Wong-Baker FACES Pain Rating Scal*e' will be used for assessing "background" pain before wound dressing change and "procedural" pain after wound dressing change (see Figure 13) (Wong-Baker 2015).

Wong and Baker have developed the '*Wong-Baker FACES Pain Rating Scale*' in the early 1980s, because children had considerable difficulty using any scales with numbers, unfamiliar words, or colours. It is reliable and valid.

8.3.5 Impact of Wounds on Sleep

In patients ≥ 14 years of age, the site study team member will ask before 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) (see Figure 14) (Blome, Baade et al. 2014).

8.3.6 Days Missed from School or Work

A site study team member will ask 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 if it was performed within less than 14 days (days missed to attend study visits will not be counted) (see Figure 15).

8.3.7 Treatment Satisfaction Questionnaire for Medication, Version 9

A site study team member will ask the patient (in patients ≥ 14 years of age) whether he/she was satisfied with the treatment using the abbreviated TSQM, Version 9 (see Figure 16) (Bharmal, Payne et al. 2009).

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

The 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 to differentiate between EB subtypes and degrees of severity (Schwieger-Briel et al. 2015).

For the clinical items five domains are evaluated (skin involvement, mucosal involvement, internal organ involvement, laboratory abnormalities, and complications/procedures). Each item contains several questions that will be used to obtain an item “score”, that will allow the calculation of a “total clinical score” by adding all individual item scores. The maximum total clinical score is a value of 114.

For the patient items seven domains are evaluated (pain, itch, essential functions, sleeping, daily activities, mood and impact). Each item contains questions that will be used to obtain an item “score”, that will allow the calculation of a “total patient score” by adding all individual item scores. The maximum total patient score is a value of 120.Clinical and patient total scores and item scores will be recorded and derived in the eCRF.

8.3.9 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 trial the EQ-5D-5L and EQ-5D-Y with 5 levels of severity will be assessed as applicable depending on the patient’s age (Herdman et al 2013, Wille et al 2010).

Both questionnaires assess several dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with a multiple choice question (five possible choices for the EQ-5D-5L, or three possible choices for the EQ-5D-Y). 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 will be recorded in the eCRF.

Figure 8 Assessment of Total Body Wound Burden based on the 'EB Disease Activity and Scarring Index' (EBDASI)

Assessment of Total Body Wound Burden based on the 'EB Disease Activity and Scarring Index' (EBDASI)

Section I: Skin

Activity

Anatomical Location	Erosions/Blisters/Crusting	Number of lesions if <3
	0 absent **1** 1-3 lesions, none ≥2 cm in any diameter **2** 1-3 lesions, at least one lesion ≥2 cm in any diameter, none >6 cm **3** >3 lesions, none >6 cm in diameter **5** >3 lesions, and/or at least one lesion ≥6 cm in diameter **7** >3 lesions, and/or at least one lesion ≥16 cm in diameter **8** almost entire area involved **10** entire area involved	
Ears		
Face		
Neck		
Chest		
Abdomen		
Back		
Arms		
Hands		
Legs		
Feet		

Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI), Section I: Skin, Activity
Used with Permission of Professor Dedee Murrell and the Australasian Blistering Diseases Foundation

EBDASI Section I: Skin, Activity Patients of all age groups **EASE Study BEB-13**

Visit: ☐D0 ☐D30 ☐D60 ☐D90 ☐M3 ☐M12 ☐M24 ENG v2

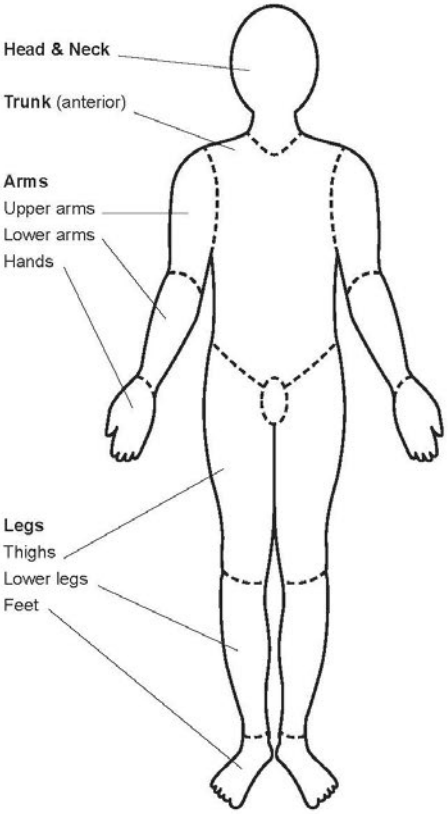
Date (DD MM YYYY): Patient No.: E 3 0

Source: (Loh, Kim et al. 2014)

Figure 9 Assessment of Body Surface Area Percentage of Total Body Surface Area Affected by EB Partial Thickness Wounds

Assessment of Body Surface affected by EB Partial Thickness Wounds

Assess the percentage of the surface area in each body region that is affected by EB partial thickness wounds and complete the table.



Region	Area % of EB partial thickness wounds
Head & Neck	%
Arms:	
- Upper	%
- Lower	%
- Hands	%
Trunk:	
- Anterior	%
- Posterior	%
Legs:	
- Thighs	%
- Lower Legs	%
- Feet	%

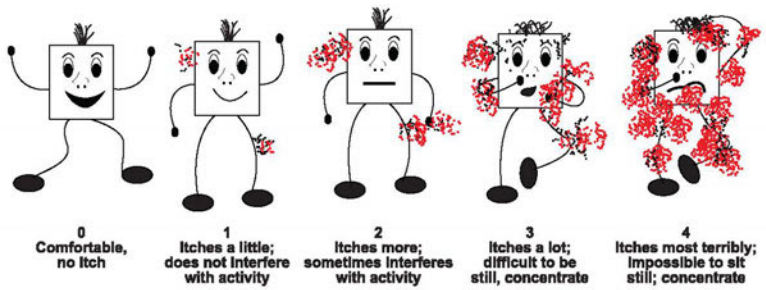
BSAP (Investigator assessment) Patients of all age groups **EASE Study BEB-13**

Visit: ☐D0 ☐D30 ☐D60 ☐D90 ☐M3 ☐M12 ☐M24 ENG v2

Date (DD MM YYYY): Patient No.: E 3 0

Source: (Miminas 2007)

Figure 10 'Itch Man Scale'



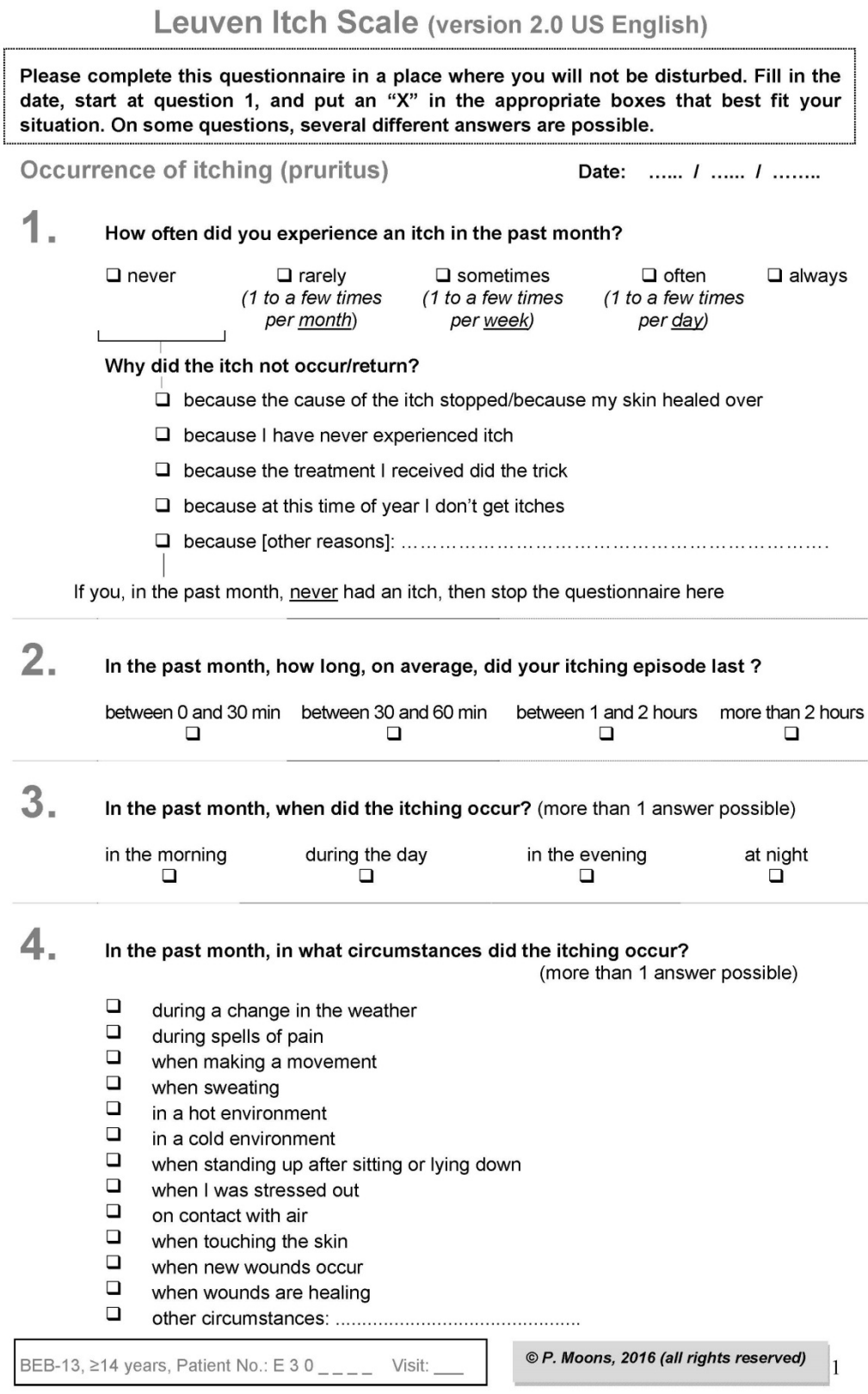
Patient age (at D0 visit): 4-13 years Visit: ☐ D0 ☐ D7 ☐ D30 ☐ D60 ☐ D90 ☐ M3 ENG v2

Itch Man Scale
EASE Study BEB-13

Date (DD MM YYYY): Patient No.: E 3 0

Source: (Morris, Murphy et al. 2012)

Figure 11 The 'Leuven Itch Scale'



Leuven Itch Scale (version 2.0 US English)

Please complete this questionnaire in a place where you will not be disturbed. Fill in the date, start at question 1, and put an "X" in the appropriate boxes that best fit your situation. On some questions, several different answers are possible.

Occurrence of itching (pruritus)

Date: ..... / ..... / .....

1. How often did you experience an itch in the past month?

❑ never | ❑ rarely *(1 to a few times per month)* | ❑ sometimes *(1 to a few times per week)* | ❑ often *(1 to a few times per day)* | ❑ always

Why did the itch not occur/return?

- ❑ because the cause of the itch stopped/because my skin healed over
- ❑ because I have never experienced itch
- ❑ because the treatment I received did the trick
- ❑ because at this time of year I don't get itches
- ❑ because [other reasons]: .....

If you, in the past month, never had an itch, then stop the questionnaire here

2. In the past month, how long, on average, did your itching episode last ?

between 0 and 30 min ❑ | between 30 and 60 min ❑ | between 1 and 2 hours ❑ | more than 2 hours ❑

3. In the past month, when did the itching occur? (more than 1 answer possible)

in the morning ❑ | during the day ❑ | in the evening ❑ | at night ❑

4. In the past month, in what circumstances did the itching occur?
(more than 1 answer possible)

- ❑ during a change in the weather
- ❑ during spells of pain
- ❑ when making a movement
- ❑ when sweating
- ❑ in a hot environment
- ❑ in a cold environment
- ❑ when standing up after sitting or lying down
- ❑ when I was stressed out
- ❑ on contact with air
- ❑ when touching the skin
- ❑ when new wounds occur
- ❑ when wounds are healing
- ❑ other circumstances: .....

BEB-13, ≥14 years, Patient No.: E 3 0 _ _ _ _ Visit: ___

1

Leuven Itch Scale (version 2.0 US English)

Severity of itching

5. **In the past month, how bad was the itching you have been experiencing?**
(Mark the bar scale below, with an "X")

No itch ——————————— Worst possible itch

Treatment of itching

6. **In the past month, how was your itching treated?** (more than 1 answer possible)

- ❑ no treatment
- ❑ with an ointment → Name: .....
- ❑ with medication → Name: .....
- ❑ otherwise: .....

7. **If you are receiving treatment, how satisfied are you with the treatment for your itching?** (Mark the bar scale below, with an "X")

Very dissatisfied ——————————— Very satisfied

Consequences of itching

8. **In the past month, what were the consequences of your itching?**

	never	rarely	some-times	often	always
1. lesions from scratching	❑	❑	❑	❑	❑
2. reduced social contact due to itching	❑	❑	❑	❑	❑
3. reduced quality of life due to itching	❑	❑	❑	❑	❑
4. disturbed my routine activities due to itching	❑	❑	❑	❑	❑
5. difficulties in falling asleep due to itching	❑	❑	❑	❑	❑
6. waking up due to itching	❑	❑	❑	❑	❑
7. needed sleeping pills due to itching	❑	❑	❑	❑	❑
8. loss of appetite due to itching	❑	❑	❑	❑	❑
9. bad mood due to itching	❑	❑	❑	❑	❑
10. changes in behavior toward others due to itching	❑	❑	❑	❑	❑
11. loss of concentration due to itching	❑	❑	❑	❑	❑
12. other consequences:.....	❑	❑	❑	❑	❑

BEB-13, ≥14 years, Patient No.: E 3 0 _ _ _ _ Visit: ___

2

Leuven Itch Scale (version 2.0 US English)

Sensory characteristics of itching

9. **In the past month, how did your itching manifest itself?**

- ❑ A tickling sensation *"as if a creepy-crawly thing was crawling over my skin"*
- ❑ A tingling sensation *"on a bitterly cold night, like stepping into a boiling hot house"*
- ❑ A prickling sensation *"like being pricked softly with a sharp object"*
- ❑ A stinging sensation *"like something piercing my skin"*
- ❑ A burning sensation *"like being on fire"*
- ❑ Another kind of sensation: .....

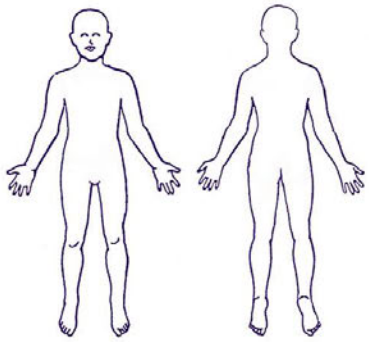
Distress of itching

10. **In the past month, how distressing was your itching?**
(Mark the bar scale below with an "X")

Not distressing at all ——————————— Very distressing

Location(s) of itching

11. **In the past month, which parts of your body itched?**
(shade the area(s) which itched)



Remarks

12. **If you have any other questions or remarks, please write them here:**

.....

.....

.....

.....

BEB-13, ≥14 years, Patient No.: E 3 0 _ _ _ _ Visit: ___

3

Source: (Haest, Casaer et al. 2011)

Figure 12 'Face, Legs, Activity, Cry, Consolability' (FLACC) Pain Rating Scale

FLACC Behavioral Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.			

☐ Background pain – pain level *before* dressing change
☐ Procedural pain – pain level *during* dressing change (assessed after dressing change)

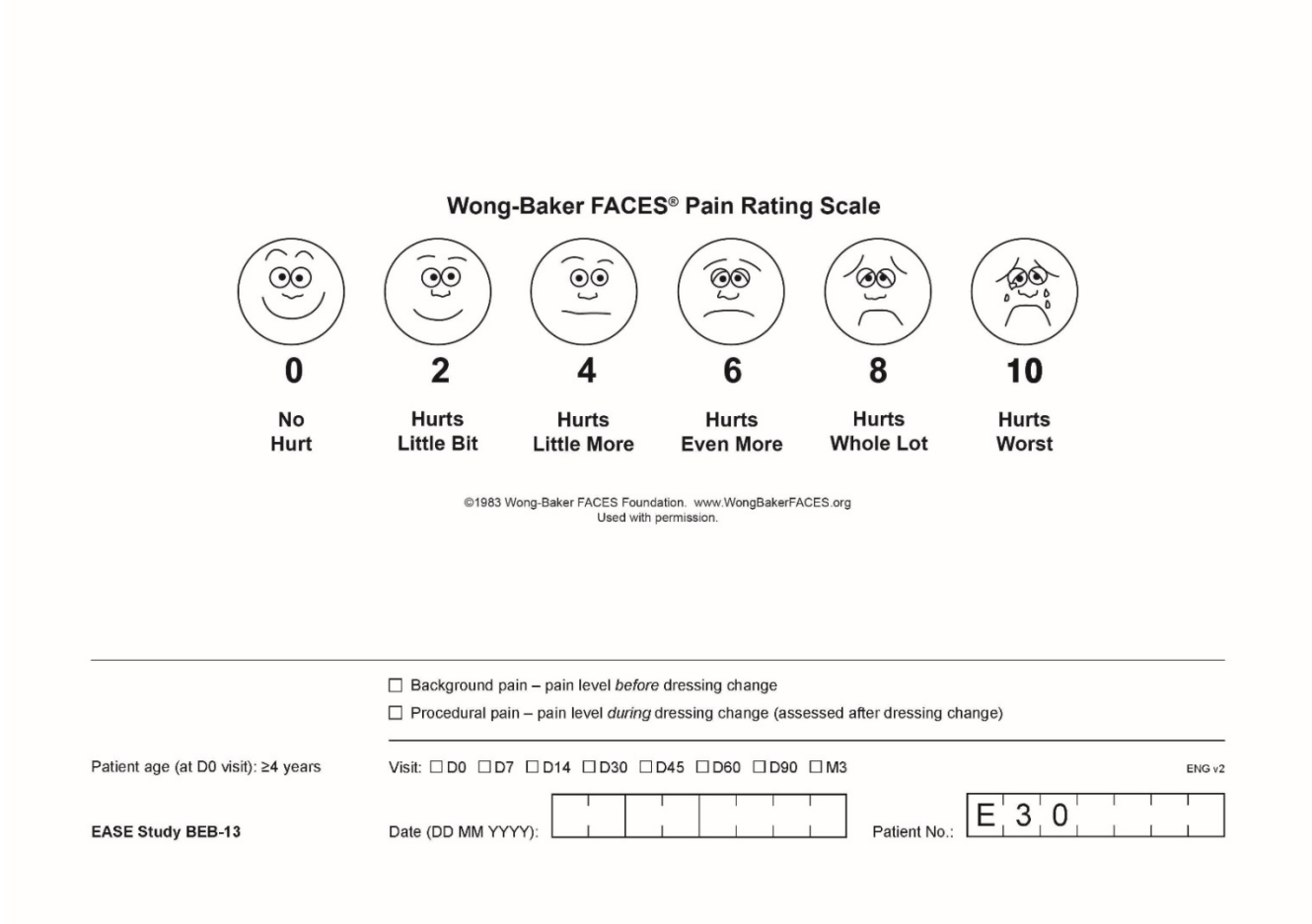
Patient age (at D0 visit): 0-3 years Visit: ☐ D0 ☐ D7 ☐ D14 ☐ D30 ☐ D45 ☐ D60 ☐ D90 ☐ M3 ENG v1

FLACC pain rating scale
EASE Study BEB-13

Date (DD MM YYYY): Patient No.: E 3 0

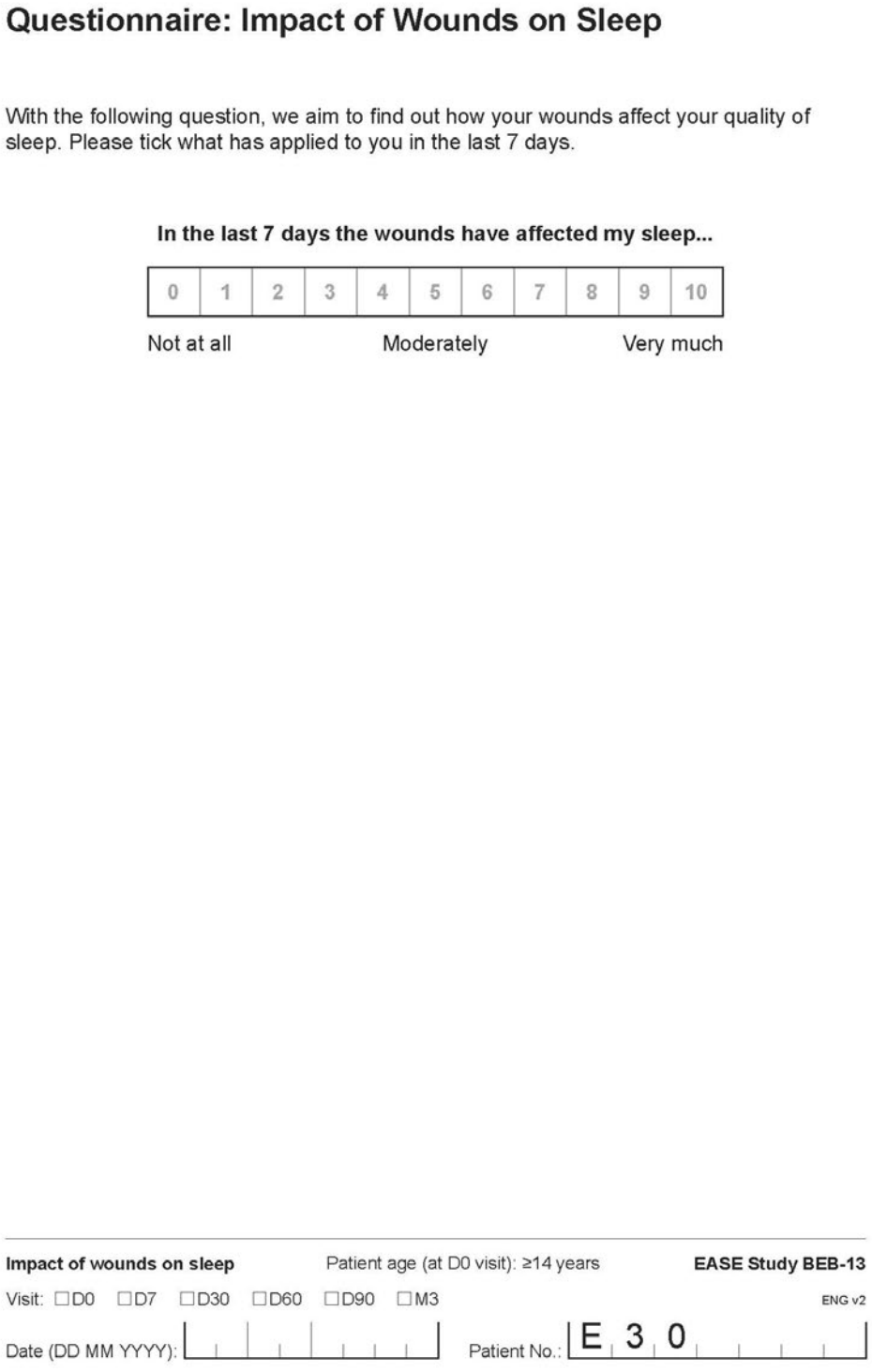
Source: (Merkel, Voepel-Lewis et al. 1997)

Figure 13 'Wong-Baker FACES®' Pain Rating Scale



Source: (Wong-Baker 2015)

Figure 14 Impact of Wounds on Sleep Based on Wound Quality of Life Questionnaire



Questionnaire: Impact of Wounds on Sleep

With the following question, we aim to find out how your wounds affect your quality of sleep. Please tick what has applied to you in the last 7 days.

In the last 7 days the wounds have affected my sleep...

0	1	2	3	4	5	6	7	8	9	10

Not at all Moderately Very much

Impact of wounds on sleep Patient age (at D0 visit): ≥14 years **EASE Study BEB-13**

Visit: ☐D0 ☐D7 ☐D30 ☐D60 ☐D90 ☐M3 ENG v2

Date (DD MM YYYY): Patient No.: E 3 0

Source: (Blome, Baade et al. 2014)

Figure 15 Days Missed from Work or School

Questionnaire: Days Missed from School or Work

The following questions ask about the effect of your EB on your ability to work or to attend school and to perform normal daily activities.
Please fill in the blanks or tick a box, as indicated.

1. **Are you currently attending school or are you employed (working for pay)?**

   ☐ NO ☐ YES

   If NO, tick "NO" and skip other questions.

   The next questions refer to the past 14 days or to the time passed since your last visit, not including today.

2. **During the past 14 days (or during the time that passed since your last visit), how many days did you miss from work or school because of problems associated with your EB?**

   ____ days

3. **During the past 14 days (or during the time that passed since your last visit), how many days did you miss from work or school because of any other reason, such as annual leave, holidays, time off to participate in this study?**

   ____ days

4. **During the past 14 days (or during the time that passed since your last visit), how many days did you actually work or attend school?**

   ____ days

Days missed from school or work Patient age (at D0 visit): ≥14 years / Parent of patient <14 years of age **EASE Study BEB-13**

Visit: ☐D0 ☐D14 ☐D30 ☐D45 ☐D60 ☐D90 ☐M3 ENG v1

Date (DD MM YYYY): ____ Patient No.: E30____

Figure 16 Treatment Satisfaction Questionnaire for Medication, Version 9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about how satisfied or dissatisfied you are with the medication you are taking in this clinical trial. We are interested in what you think about the effectiveness, side effects, and convenience experienced when using the medication over the last two to three weeks, or since you last used it. For each question, please place one tick next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

 Confidential 1/3

TSQM-9, UK English Patient age (at D0 visit): ≥14 years **EASE Study BEB-13**

Visit: ☐D7 ☐D30 ☐D60 ☐D90 ☐M3 ENG v1

Date (DD MM YYYY): | | | | | | | | Patient No.: E 3 0 | | | |

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

 Confidential 2/3

TSQM-9, UK English Patient age (at D0 visit): ≥14 years **EASE Study BEB-13**

Visit: ☐D7 ☐D30 ☐D60 ☐D90 ☐M3 ENG v1

Date (DD MM YYYY): Patient No.: E 3 0

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

 Confidential 3/3

TSQM-9, UK English Patient age (at D0 visit): ≥14 years **EASE Study BEB-13**

Visit: ☐D7 ☐D30 ☐D60 ☐D90 ☐M3 ENG v1

Date (DD MM YYYY): Patient No.: E 3 0

Source: (Bharmal, Payne et al. 2009)

Figure 17 iscorEB, September 2015

ID: ___ DOB (dd/mm/yyyy):__/__/_____ Male/Female Ass. Date (dd/mm/yyyy):__/__/_____

iscorEB: CLINICIAN SUBSCORE (max 138)					
A. SKIN INVOLVEMENT (score for each affected region)					
Characteristics	Value	Head and neck	Upper extremity	Trunk	Lower extremity
Intact blisters	1				
Erosions/denuded skin	1				
Crusting/Scabbing	1				
Chronic wounds (≥6 wks)	4				
Infections *(at least one wound with ≥3 of expanding borders, local pain, increased local temperature, purulent exudate, foul odor)*	6				
A1 skin characteristic subscore					
Weighing factor (wf) ** for patients ≤8 years*		0.1 **0.2*	0.2 **0.2*	0.3 **0.3*	0.4 **0.3*
A2 subscore (A1X wf)					
A3 subscore (Surface area affected %)	Value				
- 1-9 %	1				
- 10-29 %	2				
- 30-49 %	3				
- 50-69 %	4				
- 70-89 %	5				
->90%	6				
A4 regional skin score (A2XA3)					
A. TOTAL SKIN INVOLVEMENT added regional skin scores				**Max 78**	**A=**
B. MUCOSAL INVOLVEMENT (present at the time of the exam and/or within the past 4 weeks)					
Location	**Characteristic**	**Value**	**Characteristic**	**Value**	
B1. Mouth	***Erosions*** - Present - Absent	 0 1	***Mouth opening*** *(distance between upper and lower incisors* _____mm - 50th ile - 10-49th ile - <9th ile	 0 1 2	
Mouth subscore					**B1=**
B2. Airway	***Stridor/hoarseness*** - Absent - 1-2 days/month - 1-2 days/week - >3 days/week	 0 1 2 3	***EB related inhaled steroids use*** - Absent - 1-2 days/month - 1-2 days/week - >3 days/week	 0 1 2 3	
Airway subscore					**B2=**
B3. Eye	***Eye redness/erosions*** - Absent - 1-2 days/month - 1-2 days/week - >3 days/week	 0 1 2 3	***Palpebral closure*** (patient supine with eye closed) - Full closure - White to inferior conjunctiva - White to cornea - White to pupil	 0 1 2 3	
Eye subscore					**B3=**
B. TOTAL MUCOSAL SCORE (mouth+ airway +eye score)				**Max 15**	**B=**
C. INTERNAL ORGAN INVOLVEMENT (within the past 6 months)					
C1. GI/Nutrition	**Characteristic**	**Value**	**Characteristic**	**Value**	

iscorEB Version 3, 2015 © SickKids Hospital

2 [iscorEB Version 3, 2015 © SickKids Hospital]

Wt (Kg):_____ Ht (cm):_____ BMI:_____	***BMI^{ile}*** - ≥50th ile - 25-49th ile - 10-24th ile - 4-9th ile - ≤3rd ile	 0 1 2 3 4	***Tube feeds*** - None - Some of the nutrition - Most of nutrition - All nutrition		 0 1 2 3	
GI/Nutrition subscore						C1=
C2. Urogenital Diagnosed with renal disease *(elevated creatinine/IgA nephropathy/obstructive uropathy)*	- No - Yes, no treatment - Yes, on medication - Yes, on dialysis/listed for transplantation	0 1 2 3	**C3. Cardiac** Diagnosed with decreased cardiac function	- No - Yes, no symptoms, no treatment - Yes, symptoms and/or treatment	0 1 2	
Urogenital subscore		C2=	**Cardiac subscore**		C3=	
C. INTERNAL ORGAN INVOLVEMENT SCORE (GI/nutrition+ cardiac + urogenital)				**Max 12**		C=

D. LABORATORY ABNORMALITIES (within the past 6 months)

Laboratory test	**Ranges**		**Value**	**Item**			**Value**	
	g/L	g/dL						
D1. *Anemia* Hb value _____g/L or g/dL	≥120 100-119 80-99 61-79 ≤60	≥12 10-11.9 8-9.9 6.1-7.9 ≤6	0 1 2 3 4	**D2. *Therapy for anemia*** - None - Oral iron - Intravenous iron - Transfusions			0 1 2 3	
Anemia subscore			D1=	**Therapy for anemia subscore**				D2=
D3. *Low albumin* Albumin value _____g/L or g/100ml	g/L	g/100ml		**D4. *Inflammation*** (select all that apply; maximum score 5 irrespective of how many items are checked)				
	≥40 30-39 21-29 ≤20	≥4 3-3.9 2.1-2.9 ≤2	0 1 2 3	ESR:_____ CRP:_____ PLT:_____ Ferritin:____	≥50mm/h ≥50mg/L ≥600X10^3/mm3 ≥250 µg/L	≥50mm/h ≥5mg/dL ≥600X10^9/L ≥250 µg/L	5	
Low Albumin subscore			D3=	**Inflammation subscore**				D4=
D. LABORATORY ABNORMALITIES SCORE (anemia+therapy+low albumin+inflammation)						**Max 15**		D=

E. COMPLICATIONS/PROCEDURES (within the past 6 months)

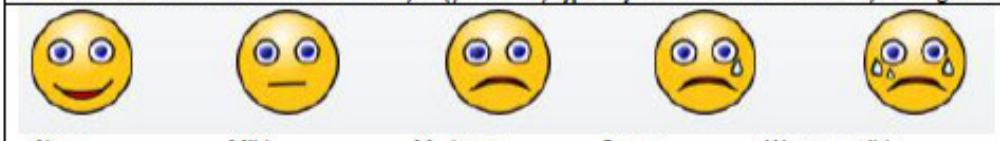
Items	**Categories**	**Value**	
E1. Squamous cell carcinoma (skin, oral or esophagus) Number:_____	- None - 1 new SCC - >2 new SCCs - nodal spread - metastatic disease	0 1 2 5 10	E1=
E2. Osteopenia/osteoporosis	- None - Normalized Z score ≥2 - Non-traumatic fractures	0 1 2	E2=
E3. Unscheduled hospital visits	- None - EB related emergency visits - EB related admission - EB related ICU admission	0 1 2 3	E3=
E4. Esophageal dilatation(s)	- None - 1-2 - 3-4 - ≥5	0 1 2 3	E4=
E. COMPLICATIONS/PROCEDURES (SCCs+ osteopenia+ hospital visits+ dilatation)		**Max= 18**	E=
iscorEB TOTAL CLINICIAN SCORE		**Max 138**	

iscorEB PATIENT SUBSCORE (max 120)

The following questions assess how much of your (your child's) life is affected by having EB. All responses range from 0 to 8; where 0 means no impact (for example if the question is about pain, 0 =no pain) to a maximum of 8 (for example if the question is about pain, 8 = the worst possible pain). There are 15 questions grouped in 7 separate categories (domains). Please provide an answer to each question by circling the number that corresponds to the best descriptor of your (your child's) status in the **past 4 weeks**.

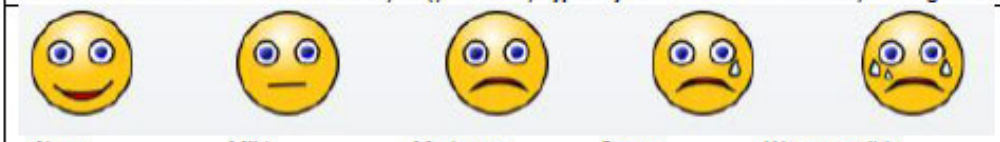
F. PAIN DOMAIN

F1. Please rate how much **OVERALL PAIN** you (your child) **typically** had *in **the last 4 weeks*** by circling one of the options below.



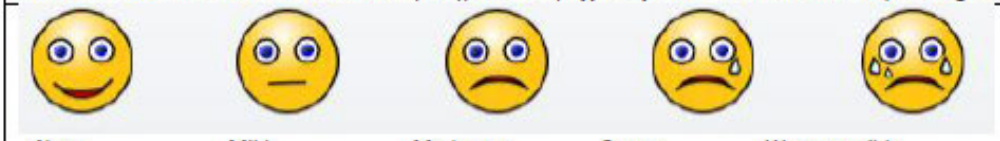
None	*Mild*	*Moderate*	*Severe*	*Worst possible*	SCORES
0	2	4	6	8	F1=

F2. Please rate how much **SKIN PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.



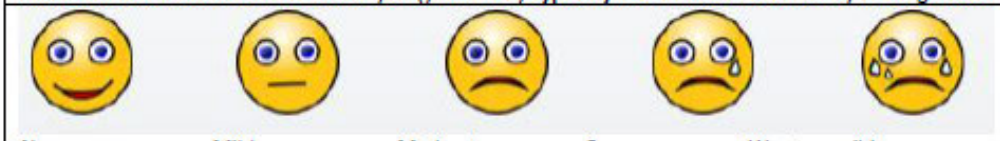
None	*Mild*	*Moderate*	*Severe*	*Worst possible*	
0	2	4	6	8	F2=

F3. Please rate how much **MOUTH PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.



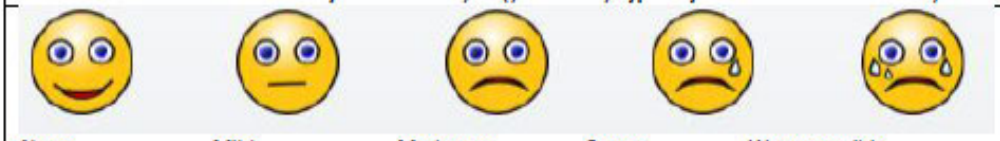
None	*Mild*	*Moderate*	*Severe*	*Worst possible*	
0	2	4	6	8	F3=

F4. Please rate how much **EYE PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.



None	*Mild*	*Moderate*	*Severe*	*Worst possible*	
0	2	4	6	8	F4=

F5. Please rate how much **BONE/JOINT PAIN** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.



None	*Mild*	*Moderate*	*Severe*	*Worst possible*	
0	2	4	6	8	F5=

G. ITCHING DOMAIN

G. Please rate how much **ITCH** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.

None	*Mild*	*Moderate*	*Severe*	*Worst possible*	
0	2	4	6	8	G=

H. ESSENTIAL FUNCTIONS DOMAIN

H1. Please rate how much **DIFFICULTY EATING/DRINKING** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.

None	*Mild*	*Moderate*	*Severe*	*Unable to drink*	
0	2	4	6	8	H1=

H2. Please rate how much **DIFFICULTY HAVING A REGULAR BOWEL MOVEMENT (BM)** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.

None	*Mild*	*Moderate*	*Severe*	*Unable to have a BM*	

4 [iscorEB Version 3, 2015 © SickKids Hospital]

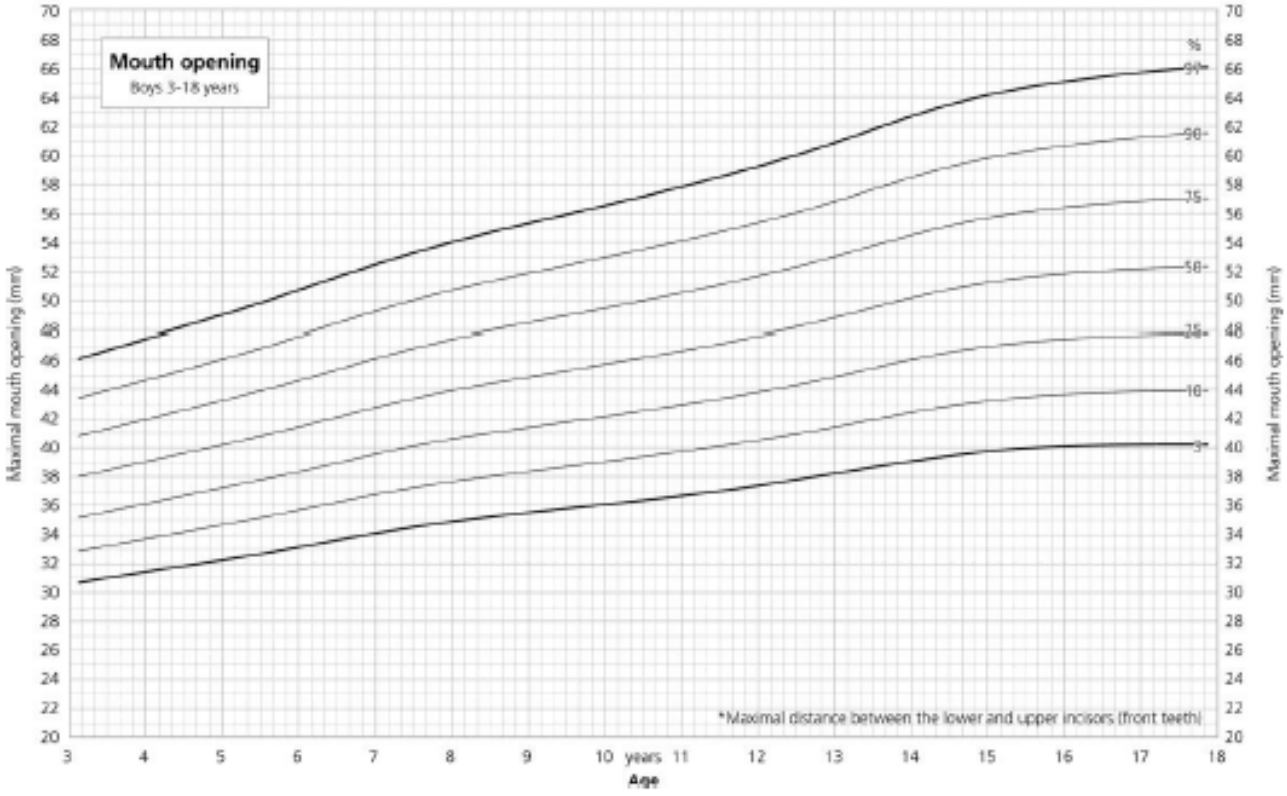
0	2	4	6	8	H2=
H3. Please rate how much **DIFFICULTY URINATING/VOIDING** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to void*	
0	2	4	6	8	H3=
I. SLEEPING DOMAIN					
I. Please rate how much **SLEEP DISTURBANCE (difficulty falling or staying asleep)** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to sleep*	
0	2	4	6	8	I=
J. DAILY ACTIVITIES DOMAIN					
J1. Please rate how much **DIFFICULTY MOVING AROUND** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to move*	
0	2	4	6	8	J1=
J2. Please rate how much **DIFFICULTY USING HANDS** you (your child) **typically** had in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to use hands*	
0	2	4	6	8	J2=
K. MOOD DOMAIN					
K. Please rate how you/your child **typically FELT** in ***the last 4 weeks*** by circling one of the options below.					
Happy	*Mostly happy*	*Somewhat unhappy*	*Unhappy*	*Very Unhappy*	
0	2	4	6	8	K=
L. IMPACT DOMAIN					
L1. Please rate how much **IMPACT ON LEISURELY ACTIVITIES** (play, relaxation, etc) your (your child's) **disease typically** had on your activities in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to do anything*	
0	2	4	6	8	L1=
L2. Please rate how much **IMPACT ON WORK/SCHOOL/LEARNING** your (your child's) **disease typically** had on your activities in ***the last 4 weeks*** by circling one of the options below.					
None	*Mild*	*Moderate*	*Severe*	*Unable to work/school/learn*	
0	2	4	6	8	L2=
PATIENT SUBSCORE (sum of all domains)				**Max 120**	

☐ Filled by patient

☐ Parent/Caregiver

Clinician Subtotal Score	
Patient Subtotal Score	
TOTAL iscorEB	

Name Date of birth



Name Date of birth

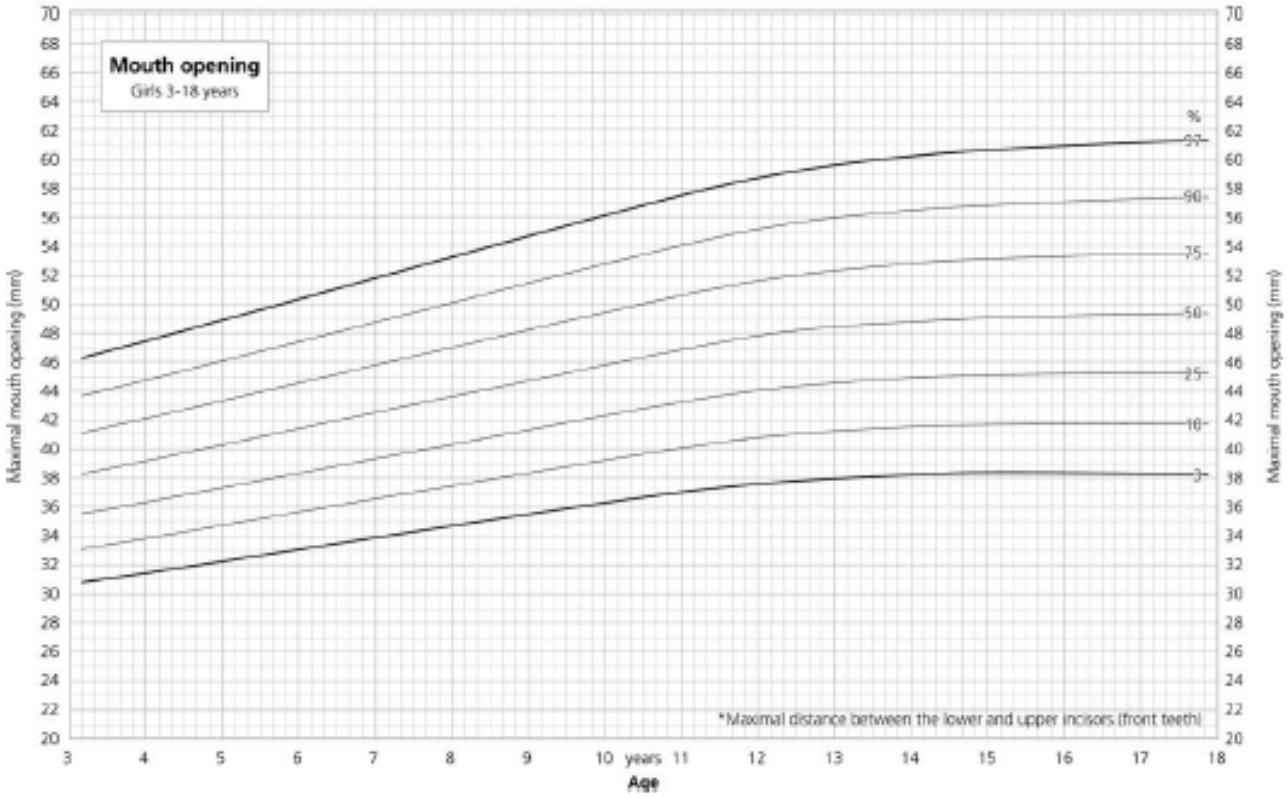


Figure 18 EQ-5D-5L, Version 1.2

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

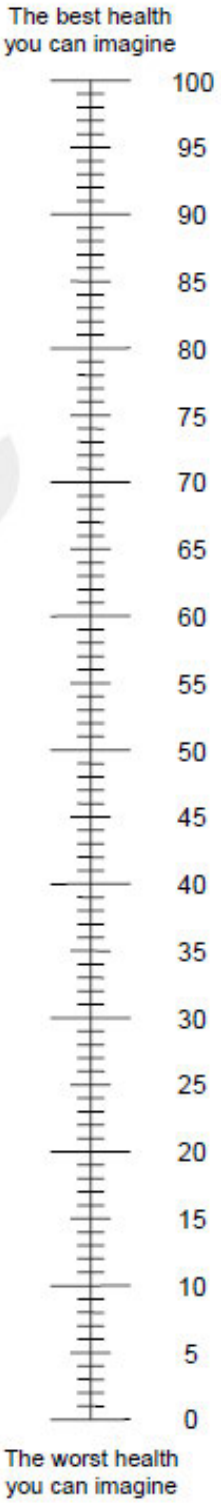
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Figure 19 EQ-5D-Y, Version 2.0

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY *(walking about)*

I have no problems walking about ❑

I have some problems walking about ❑

I have a lot of problems walking about ❑

LOOKING AFTER MYSELF

I have no problems washing or dressing myself ❑

I have some problems washing or dressing myself ❑

I have a lot of problems washing or dressing myself ❑

DOING USUAL ACTIVITIES *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

HAVING PAIN OR DISCOMFORT

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

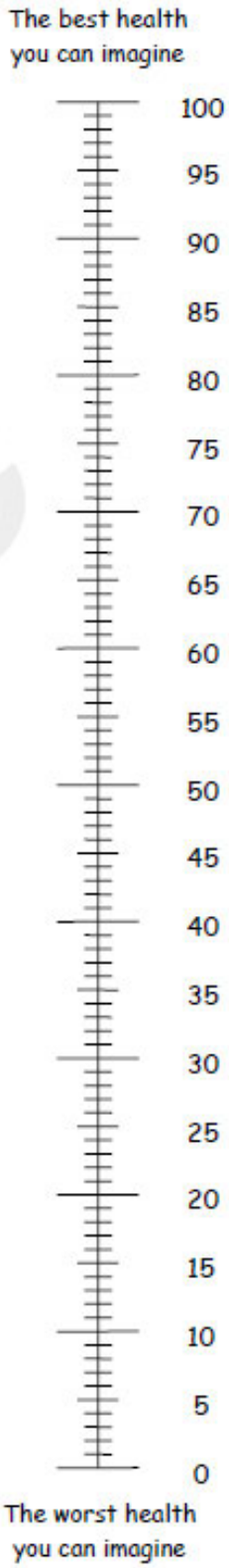
FEELING WORRIED, SAD OR UNHAPPY

I am not worried, sad or unhappy ❑

I am a bit worried, sad or unhappy ❑

I am very worried, sad or unhappy ❑

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line that shows how your health is TODAY.



9 VISIT SCHEDULE

The visit schedule is summarised in Section 1.2 *Flow Chart of Study (Randomised, Double-blind and Open-label Follow-up).* Figure 20 displays the assessments by visit during the randomised DBP and Figure 21 shows the assessments by visit during the open-label FU. The proposed chronology of efficacy assessments by visit is summarised in Figure 22.

The calculation of all study days is based on D0, which is defined as the day of the first application of study medication for the randomised DBP and the day of the first application of study medication for the open-label FU phase.

9.1 Screening, Enrolment, and Stratified Randomisation (≤D0)

During screening, study sites might contact patients who are registered in centre-specific databases to inform them about the study and to invite them for screening. If applicable informed consent may be obtained. During screening, the optional informed consent for collection of blood samples for betulin analysis and the optional consent for genetic testing to determine EB subtype will be discussed with the patient.

At baseline on D0 of the DBP, if the informed consent has not been collected at screening, the investigator will have to obtain written informed consent from the patient or legal study representative(s) before any study-related procedure will be initiated. If the patient consents to the optional collection of blood samples for betulin analysis, written consent will also 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.

All patients who sign the study-specific informed consent form will be recorded on the Screening Log. The patients will be identified by a code of letters and numbers during screening. Only those patients who will have met all eligibility criteria will be assigned a patient number (please refer to Section 7.1.1 *Treatment Assignment/Blinding Procedure*), and will be documented on the enrolment log.

The patient number is a 1-letter, 6-digit number. The letter identifies the study, the first 4 digits identify the study site, and the last 2 digits identify the patients in the sequence they enter the study (assigned by the investigator at the study site). If a patient is screened, but not enrolled into the study, the reason for screening failure will be recorded.

9.1.1 Screening Assessments

During the screening visit, the following will be completed:

- Confirmation of patient eligibility using the inclusion criteria (see Section 5.1 *Inclusion Criteria*) and exclusion criteria (see Section 5.2 *Exclusion Criteria*)
- A blood sample will be taken for haematology (full blood count with white blood cell differential), biochemistry panels (Na, K, Ca, Cl, P, BG) including renal (urea, creatinine), and hepatic function tests (serum total protein, albumin, ALT, AST, GGT, and AP), and betulin levels. This sample can alternatively be taken at baseline (D0).
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents

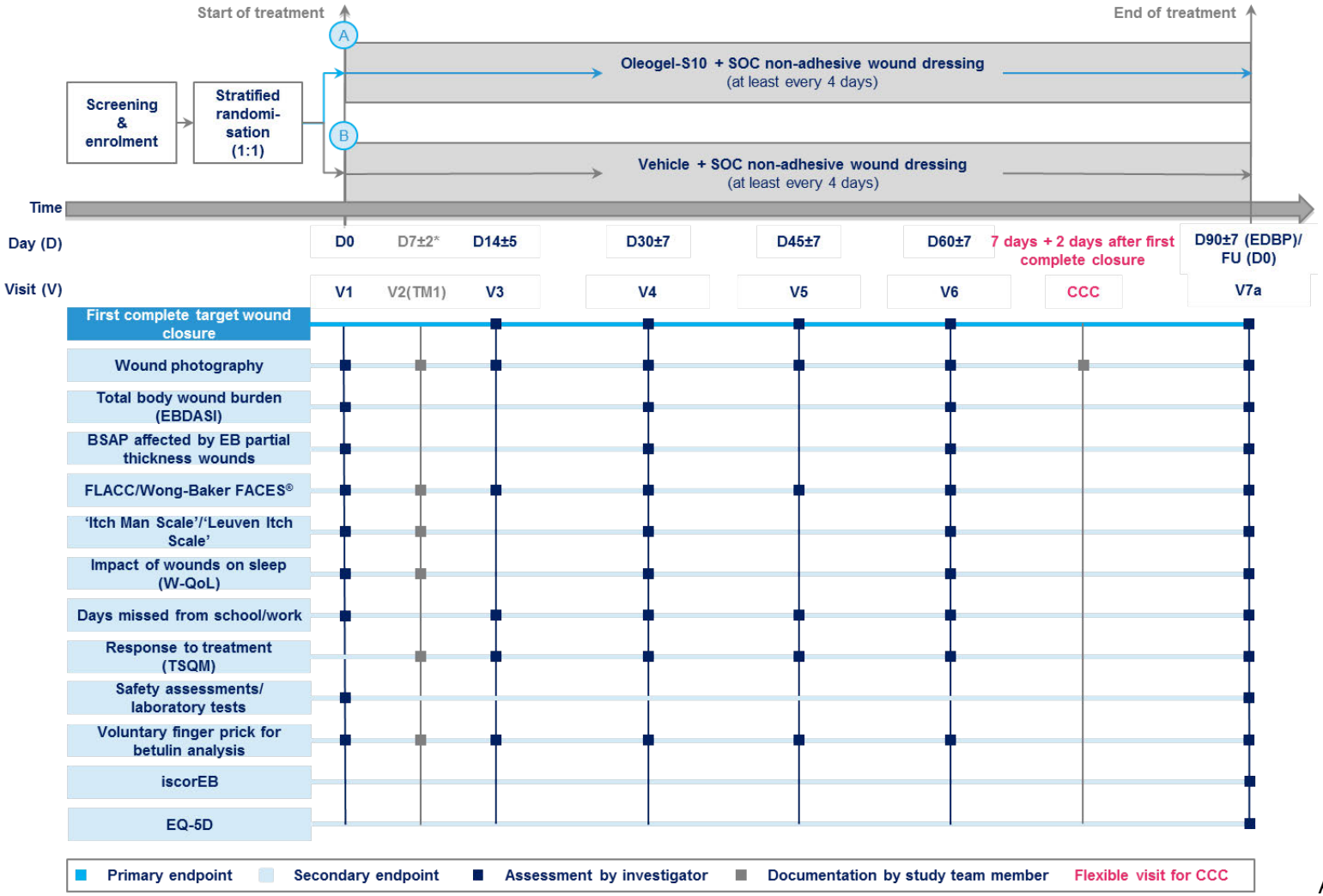
9.1.2 Enrolment and Stratified Randomisation

If the patient meets all eligibility criteria, the investigator will stratify the patient according to his/her EB subtype and target wound size (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. The site will proceed with the centralised randomisation procedure as described in Section 7.1.1 *Treatment Assignment/Blinding Procedure*.

9.1.3 Rescreening

If the patient is a screen failure, the patient can be rescreened if he/she later becomes eligible, as deemed appropriate by the investigator. The patient must be reconsented, and all screening procedures must be repeated. The patient will receive a new patient number in the database.

Figure 20 Study Schema – Double-blind Phase

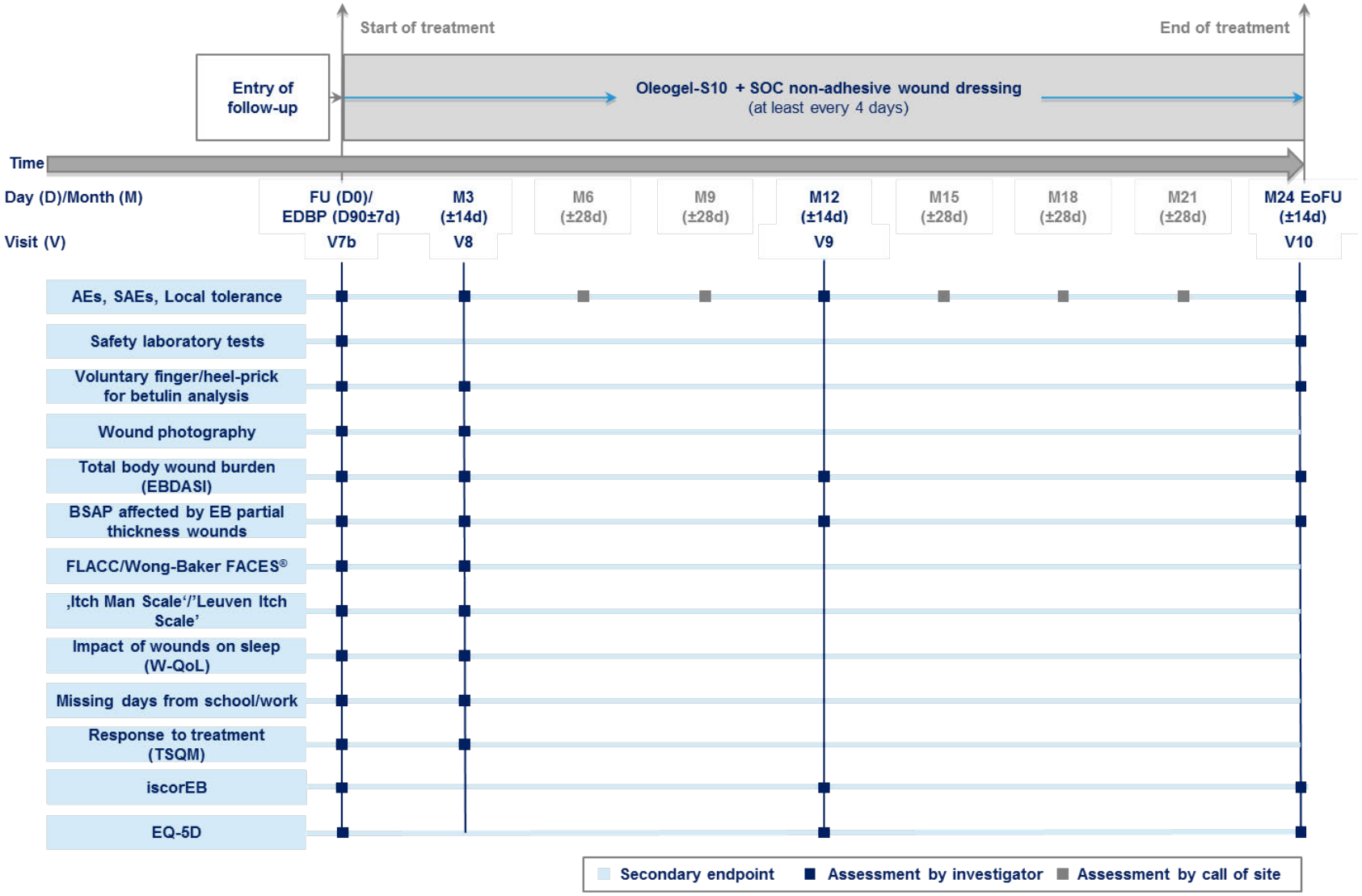


Amryt Pharma Figure

* D7±2 may be a phone call instead of a site or home visit. If the patient has a phone call the photography, patient-reported outcomes, and voluntary blood sample will not be performed.

AEs = Adverse event(s); BSAP = Body surface area percentage; CCC = Confirmation of complete closure (of EB target wound); D = Day; EB = Epidermolysis Bullosa; EBDASI = Epidermolysis Bullosa Disease Activity and Scarring Index; EDBP = End of Double-blind Phase; EQ-5D = EuroQol 5 Dimensions; FLACC = 'Face, Legs, Activity, Cry, Consolability'; iscorEB = Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa; SAEs = Serious adverse events; SOC = Standard of care; TSQM = Treatment Satisfaction Questionnaire for Medication; V = Visit; W-QoL = Wound Quality of Life Questionnaire.
Sources: BSAP affected by EB partial thickness wounds based on the 'Lund and Browder' chart (Miminas 2007); EBDASI (Loh, Kim et al. 2014); EQ-5D (Herdman et al 2013, Wille et al 2010); FLACC (Merkel, Voepel-Lewis et al. 1997); iscorEB (Schwieger-Briel et al 2015); 'Itch Man' Scale (Morris, Murphy et al. 2012); 'Leuven Itch Scale' (Haest, Casaer et al. 2011); Treatment Satisfaction Questionnaire for Medication (Bharmal, Payne et al. 2009); 'Wong-Baker FACES®' (Wong-Baker 2015); 'W-QoL' (Blome, Baade et al. 2014)

Figure 21 Study Schema – Open-label Follow-up Phase



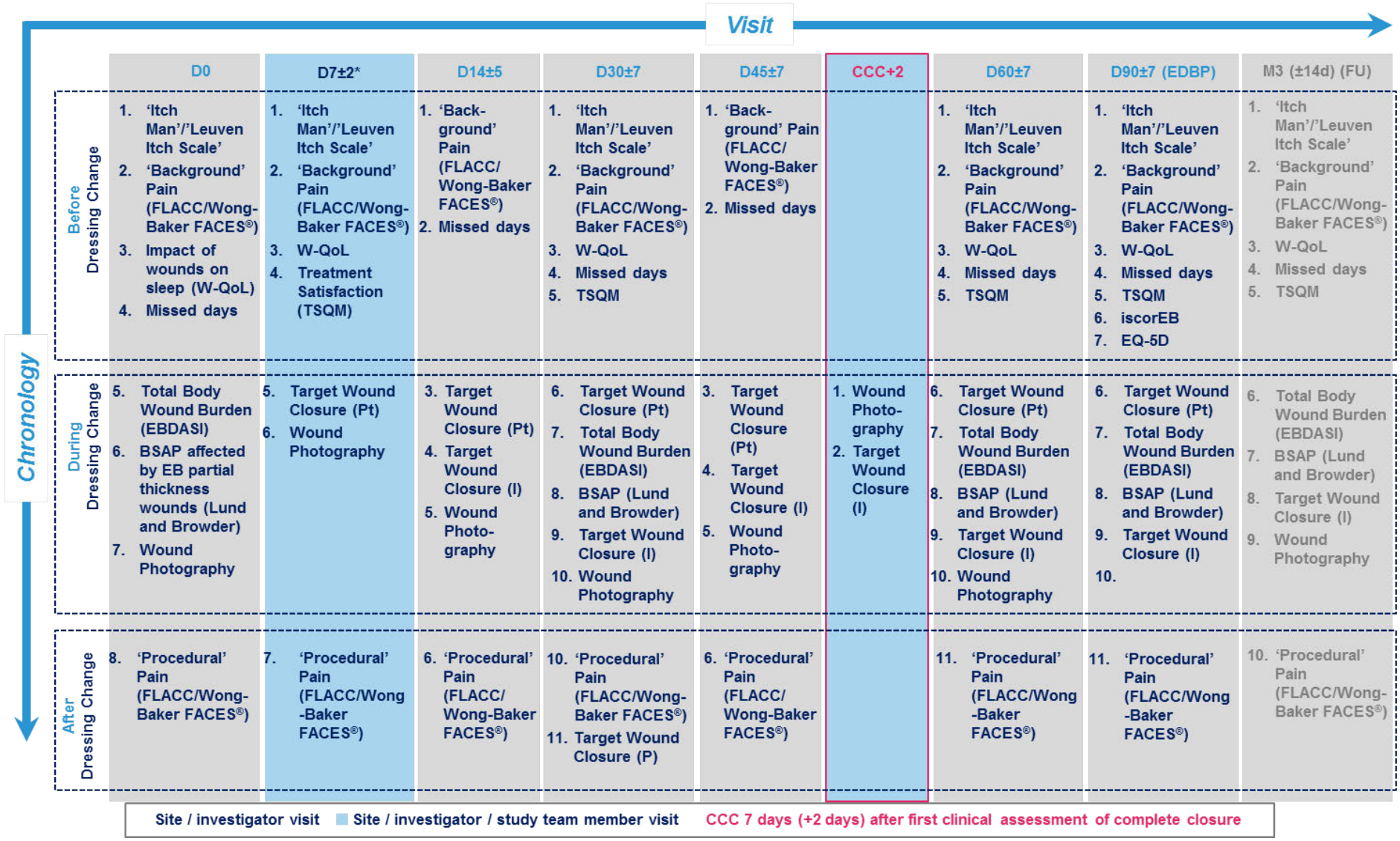
*** Urine pregnancy test only in women of childbearing potential/postmenarchal female adolescent patients**

Amryt Pharma Figure

AEs = Adverse event(s); BSAP = Body surface area percentage; D = day; d = Days; EB = Epidermolysis bullosa; EBDASI = Epidermolysis Bullosa Disease Activity and Scarring Index; EQ-5D = EuroQol 5 Dimensions; EoFU = End of Follow-up; FLACC = 'Face, Legs, Activity, Cry, Consolability'; iscorEB = Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa; SAEs = Serious adverse event(s); SOC = Standard of care; TSQM = Treatment Satisfaction Questionnaire for Medication; V = Visit; W-QoL = Wound Quality of Life Questionnaire

Sources: BSAP affected by EB partial thickness wounds based on the 'Lund and Browder' chart (Miminas 2007); EBDASI (Loh, Kim et al. 2014); EQ-5D (Herdman et al 2013, Wille et al 2010); FLACC (Merkel, Voepel-Lewis et al. 1997); iscorEB (Schwieger-Briel et al 2015); 'Itch Man' Scale (Morris, Murphy et al. 2012); 'Leuven Itch Scale' (Haest, Casaer et al. 2011); Treatment Satisfaction Questionnaire for Medication (Bharmal, Payne et al. 2009); 'Wong-Baker FACES®' (Wong-Baker 2015); 'W-QoL' (Blome, Baade et al. 2014)

Figure 22 Chronology of Efficacy Assessments by Visit



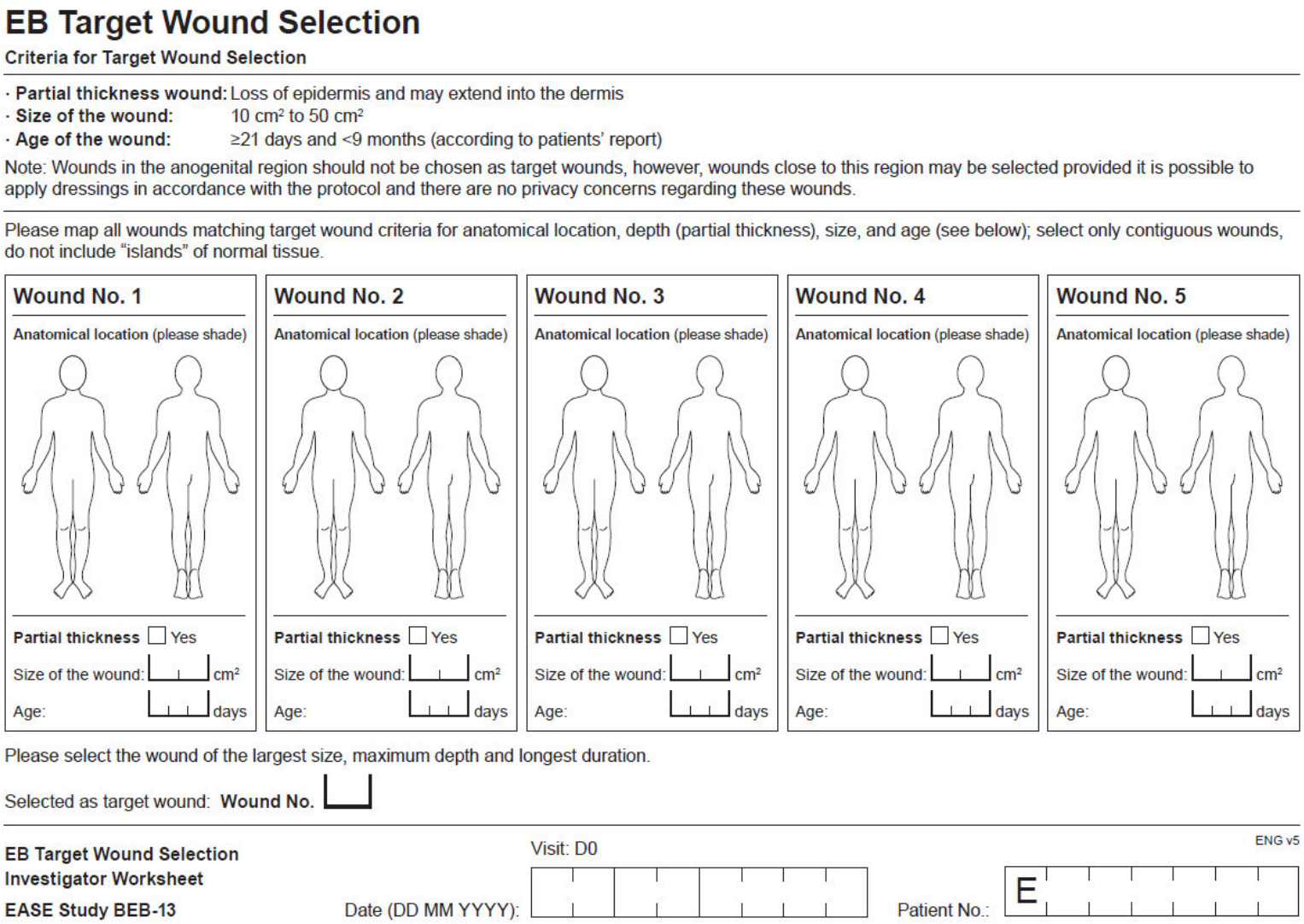
Amryt Pharma Figure

* D7±2 may be a phone call instead of a site or home visit. If the patient has a phone call efficacy assessment will not be performed

BSAP = Body surface area percentage; CCC = Confirmation of complete closure (of the EB target wound); D = Day; d = Days; EB = Epidermolysis Bullosa; EBDASI = Epidermolysis Bullosa Disease Activity and Scarring Index; EDBP = End of Double-blind Phase; EQ-5D = EuroQol 5 Dimensions; FLACC = 'Face, Legs, Activity, Cry, Consolability'; FU = Follow-up; I = Investigator; iscorEB = Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa; M = Month; Pt = Patient; TSQM = Treatment Satisfaction Questionnaire for Medication; W-QoL = Wound Quality of Life Questionnaire

Sources: BSAP affected by EB partial thickness wounds based on the 'Lund and Browder' chart (Miminas 2007); EBDASI (Loh, Kim et al. 2014); EQ-5D (Herdman et al 2013, Wille et al 2010); FLACC (Merkel, Voepel-Lewis et al. 1997); iscorEB (Schwieger-Briel et al 2015); 'Itch Man' Scale (Morris, Murphy et al. 2012); 'Leuven Itch Scale' (Haest, Casaer et al. 2011); Treatment Satisfaction Questionnaire for Medication (Bharmal, Payne et al. 2009); 'Wong-Baker FACES®' (Wong-Baker 2015); Wound-QoL' (Blome, Baade et al. 2014)

Figure 23 Example of Investigator's Worksheet



EB Target Wound Selection

Criteria for Target Wound Selection

- **Partial thickness wound:** Loss of epidermis and may extend into the dermis
- **Size of the wound:** 10 cm² to 50 cm²
- **Age of the wound:** ≥21 days and <9 months (according to patients' report)

Note: Wounds in the anogenital region should not be chosen as target wounds, however, wounds close to this region may be selected provided it is possible to apply dressings in accordance with the protocol and there are no privacy concerns regarding these wounds.

Please map all wounds matching target wound criteria for anatomical location, depth (partial thickness), size, and age (see below); select only contiguous wounds, do not include "islands" of normal tissue.

Wound No. 1	Wound No. 2	Wound No. 3	Wound No. 4	Wound No. 5
Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)
Partial thickness ☐ Yes	**Partial thickness** ☐ Yes	**Partial thickness** ☐ Yes	**Partial thickness** ☐ Yes	**Partial thickness** ☐ Yes
Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²
Age: ___ days	Age: ___ days	Age: ___ days	Age: ___ days	Age: ___ days

Please select the wound of the largest size, maximum depth and longest duration.

Selected as target wound: **Wound No.** ___

EB Target Wound Selection
Investigator Worksheet
EASE Study BEB-13

Visit: D0

Date (DD MM YYYY): ___

Patient No.: E ___

ENG v5

9.2 Double-blind Phase (Visits 1 to 7a)

9.2.1 Visit 1 (Site Visit at D0)

The following assessments will be completed and treatment with study medication will be initiated as follows:

Before wound dressing change

- Demographic data (age, gender, ethnic origin, Fitzpatrick skin type, height, weight), medical history and current medical conditions, and EB subtype as evidenced by date and method of diagnosis (e.g., genetic analysis, immunofluorescence mapping, transmission electron microscopy)
- A physical examination and selection of the EB target wound as described in the '*Investigator's Worksheet*' (see Figure 23)
- Vital signs: heart rate, respiratory rate, and body temperature
- ECG
- A record of concomitant medication
- Enquire about any AEs/SAEs and record them on the Medical History/Current Medical Conditions section in the eCRF
- Patients ≥ 4 years and up to 13 years of age to will be asked to assess itch using the '*Itch Man Scale'* (Morris, Murphy et al. 2012). Patients ≥ 14 years of age will use the *'Leuven Itch Scale'* Version 2.0 (see Section 8.3.1 '*Itch Man Scale'* and Figure 10 as well as Section 8.3.2 '*Leuven Itch Scale*' and Figure 11).
- The investigator or delegated site study team member will assess "background" pain using the FLACC scale (Merkel, Voepel-Lewis et al. 1997) in patients <4 years of age (see Section 8.3.3 *'Face, Legs, Activity, Cry, Consolability' Pain Rating Scale* and Figure 12). In patients ≥ 4 years of age the 'Wong-Baker FACES Pain Rating Scale' (Wong-Baker 2015) will be used (see Section 8.3.4 *Wong-Baker FACES Pain Rating Scale* and Figure 13).
- Patients ≥ 14 years of age will be asked "whether the wounds have affected their sleep within the last 7 days" using an 11-point Likert scale (Blome, Baade et al. 2014).
- Patients ≥ 14 years of age or a parent of patients <14 years of age will be asked "how many days have been missed from school or from work due to EB in the last 14 days".
- A blood sample will be taken for haematology (full blood count with white blood cell differential), biochemistry panels (Na, K, Ca, Cl, P, BG) including renal (urea, creatinine), and hepatic function tests (serum total protein, albumin, ALT, AST, GGT, and AP), and betulin levels at baseline. If haematology and biochemistry parameters have been determined within 4 weeks prior to this visit, they might be used as baseline values instead. If blood samples for haematology and biochemistry parameters are not taken at this visit, and if the patient consents, a blood sample will be taken for betulin analysis. Note: Blood sampling needs to occur prior to study medication exposure.
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents. If performed within 14 days prior to baseline it does not need to be repeated.

After removal of wound dressings

- An investigator will assess total body wound burden using Section I of the EBDASI (see Figure 8) (Loh, Kim et al. 2014).
- The investigator will assess the BSAP of TBSA affected by EB partial thickness wounds based on the '*Lund and Browder*' chart (see Figure 9) (Miminas 2007).
- An investigator or delegated site study team member will photo-document the target wound and all other wounds that match target wound criteria with the ARANZ Silhouette®

system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds.*

- The patient will be randomised to receive Oleogel-S10 or the vehicle as described in Section 7.1.1 *Treatment Assignment/Blinding Procedure*. The study medication will be dispensed to the patient or the patient's parent/legal guardian.
- The investigator or delegated site study team member will apply the assigned treatment and train the patient or the patient's parent/legal guardian in the application of the study medication.
- The patient or the patient's parent/legal guardian will be asked how frequently he/she plans to change wound dressings in the following weeks.

After wound dressing change

- In patients <4 years of age, "procedural" pain during wound dressing change will be assessed by the site study team member using the FLACC scale (Merkel, Voepel-Lewis et al. 1997). Patients ≥ 4 years of age will be asked to assess "procedural pain" during wound dressing change using the *'Wong-Baker FACES Pain Rating Scale'* (Wong-Baker 2015).
- The patient or the patient's parent/legal guardian will be instructed to call the site if he/she observes closure of the target wound at any time during the study. If a patient or the patient's parent/legal guardian observes target wound closure, the next visit should be arranged for as early as possible within the visit window.

9.2.2 Visit 2 (Site Visit, Home Visit, or Phone Call by Study Team Member at D7±2)

The patient will visit the site or a site study team member (e.g., study nurse) will visit the patient at home on D7±2. Alternatively, the patient will receive a phone call from a site study team member on D7±2 for:

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- The evaluation of itch as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessments of "background" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).**
- The evaluation of impact of wounds on sleep (in patients ≥ 14 years of age) as described in Section 9.2.1 *Visit 1 (Site Visit at D0).**
- The assessment of treatment response (in patients ≥ 14 years of age) using the TSQM as described in Section 8.3.7 *Treatment Satisfaction Questionnaire for Medication, Version 9.**
- If the patient consents, a blood sample will be taken for betulin analysis. Note: Blood draw needs to occur prior to study medication exposure.*

After removal of wound dressings

- The assessment of first closure of the EB target wound from the patient's point of view.
- Photography of the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds**.
- Observation of and, if wished by the patient, assistance in wound dressing change and the application of study medication.*
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

After wound dressing change

- The assessment of "procedural" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).**

* Assessment will be performed if patient has site visit or home visit. If the patient has phone call, the assessment will not be performed.

9.2.3 Visit 3 and Visit 5 (Site Visit or Home Visit by Investigator at D14±5 and D45±7)

The patient will visit the site at D14±5 and D45±7. Alternatively, the investigator may visit the patient at home at D14±5 and D45±7.

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- The assessment of "background" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of "how many days have been missed from school or from work due to EB in the last 14 days" as described in Section 9.2.1 *Visit 1 (Site Visit at D0)*.
- If the patient consents, a blood sample will be taken for betulin analysis. Note: Blood draw needs to occur prior to study medication exposure.

After removal of wound dressings

- The assessment of first closure of the EB target wound from the patient's point of view.
- The clinical assessment of the target wound for closure (performed by an investigator).
- Photography of the target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system as described in Section 8.2.1 P*hotography of EB Target Wound and Other Wounds.*
- Observation of and, if wished by the patient, assistance in wound dressing change and the application of study medication.
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

After wound dressing change

- The assessments of "procedural" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- Study medication will be reviewed. All used and unused medication will be returned and the unused tubes will be redispensed. Additional study medication will be dispensed as required. For drug accountability, the number of used and unused tubes will be counted and used kits will be weighed.

9.2.4 Visit 4 and Visit 6 (Site Visit at D30±7 and D60±7)

The patient will visit the site at D30±7 and at D60±7.

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- The evaluation of itch as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessments of "background" pain and "procedural" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The evaluation of impact of wounds on sleep (in patients ≥ 14 years of age) as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*

- The assessment of "how many days have been missed from school or from work due to EB in the last 14 days" as described in Section 9.2.1 *Visit 1 (Site Visit at D0)*.
- The assessment of treatment response (in patients ≥ 14 years of age) using the TSQM as described in Section 8.3.7 *Treatment Satisfaction Questionnaire for Medication, Version 9.*
- If the patient consents, a blood sample will be taken for betulin analysis. Note: Blood sampling needs to occur prior to study medication exposure.

After removal of wound dressings

- The assessment of first closure of the EB target wound from the patient's point of view.
- The assessment of total body wound burden as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of BSAP of TBSA affected by EB partial thickness wounds as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The clinical assessment of the target wound for closure (performed by an investigator).
- Photography of the target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds.*
- Observation of and, if wished by the patient, assistance in wound dressing change and the application of study medication.
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

After wound dressing change

- The assessment of "procedural" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0)*
- Study medication will be reviewed. All used and unused medication will be returned and the unused tubes will be redispensed. Additional study medication will be dispensed as required. For drug accountability, the number of used and unused tubes will be counted and used kits will be weighed.

9.2.5 'Confirmation of Complete Closure' Visit (Flexible Site Visit or Home Visit by Study Team Member 7 days [+2 Days] After First Complete Closure of the EB Target Wound in the Double-blind Phase)

A site study team member (e.g., study nurse) will visit the patient at home 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound (based on clinical assessment by an investigator at a scheduled visit) for confirmation of complete closure (CCC) of EB target wound. Alternatively, the patient will visit the site 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound for CCC. Adverse events/SAEs, local tolerability, and concomitant medication will be recorded. If the patient consents, a blood sample will be taken for betulin analysis. Note: Blood draw needs to occur prior to study medication exposure. The target wound will be photo-documented with the ARANZ Silhouette® system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds*. Photographs will be reviewed by the investigator. Wound dressings will be changed, and the study medication will continue to be applied to any remaining EB wounds matching target wound criteria. It is not necessary to continue to apply study medication to the closed wound.

9.3 Unscheduled Visits

Unscheduled visits should be performed whenever necessary (e.g., in case of AEs or SAEs).

Evaluations and/or assessments should be performed as deemed appropriate by the investigator based on the nature of the event prompting an unscheduled visit.

The results of all examinations during an unscheduled visit should be documented in the patient's file and should be recorded in the eCRF. If a patient discontinues the study prematurely during the DBP, the EDBP (D90±7) visit assessments should be performed (see Section 9.4 *Visit 7a [Site Visit at D90±7] End of Double-blind Phase*). If a patient discontinues the FU phase prematurely, the assessments scheduled for the EoFU (M24±14 Days) visit should be performed (see Section 9.5.5 *End of Follow-up Visit 10 [M24±14 Days]*).

9.4 Visit 7a (Site Visit at D90±7): End of Double-blind Phase/ Premature Discontinuation of Double-Blind Phase

The patient will visit the site for the EDBP visit at D90±7. The EDBP visit should also be performed at any time if the patient is prematurely discontinued from the DBP of the study.

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- A physical examination will be performed.
- Vital signs such as heart rate, respiratory rate, and body temperature will be recorded.
- ECG.
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents.
- The evaluation of itch as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessments of "background" pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The evaluation of impact of wounds on sleep (in patients ≥ 14 years of age) as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of "how many days have been missed from school or from work due to EB in the last 14 days" as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of treatment response (in patients ≥ 14 years of age) using the TSQM as described in Section 8.3.7 *Treatment Satisfaction Questionnaire for Medication, Version 9.*
- The assessment of disease severity from both clinician and patient/family perspective using the iscorEB (only when available in the local language) as described in Section 8.3.8.
- The assessment of health-related quality of life using the EQ-5D instrument as described in Section 8.3.9.
- A blood sample will be taken for haematology (full blood count with white blood cell differential), biochemistry panels (Na, K, Ca, Cl, P, BG) including renal (urea, creatinine), and hepatic function tests (serum total protein, albumin, ALT, AST, GGT, and AP), and betulin levels.
- All used and unused study medication will be returned. For drug accountability, the number of used and unused tubes will be counted and used kits will be weighed.

After removal of wound dressings

- The assessment of first closure of the EB target wound from the patient's point of view.
- The assessment of total body wound burden as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of BSAP of TBSA affected by EB partial thickness wounds as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The clinical assessment of the target wound for closure (performed by an investigator).
- Photography of the target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds*.

- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

Once the EDBP visit is complete and all study medication is returned, the patient will enter the single-arm, open-label FU phase. Visit 7b will performed as part of the same visit as Visit 7a and open-label study medication will be applied in Visit 7b (see Section 9.5.1 *Visit 7b [in Conjunction with Visit 7a at D90±7])*.

9.5 Open-label Follow-up Phase

The patients will be asked to call the study site if any AEs or unexpected events occur between the site visits or site calls.

9.5.1 Visit 7b (in Conjunction with Visit 7a at D90±7)

The EDBP visit at D90±7 corresponds to the D0 of the open-label FU. The data of EB total body wound burden and BSAP assessment at EDBP (D90±7) will be used as baseline data of D0 of the FU.

Following completion of the EDBP visit (Visit 7a), the patient will continue to D0 of the open-label FU:

After removal of wound dressings

- The open-label FU study medication will be dispensed to the patient.
- Observation of and, if wished by the patient, assistance in wound dressing change. The open-label phase study medication will be applied.

After wound dressing change

- The assessment of “procedural” pain as described in Section 9.2.1 *Visit 1 (Site Visit at* D0).

9.5.2 Visit 8 (Site Visit M3±14 Days)

The patient will come in for a site visit at M3±14 days for:

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents.
- The evaluation of itch as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of “background” pain as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The evaluation of impact of wounds on sleep (in patients ≥ 14 years of age) as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The evaluation of days missed from school or from work as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of treatment response (in patients ≥ 14 years of age) using the TSQM as described in Section 8.3.7 *Treatment Satisfaction Questionnaire for Medication, Version 9.*
- If the patient consents, a blood sample for betulin analysis. Note: Blood sampling needs to occur prior to study medication exposure.

After removal of wound dressings

- The assessment of total body wound burden as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of BSAP of TBSA affected by EB partial thickness wounds as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*

- The clinical assessment of the target wound for closure (performed by an investigator).
- Photography of the target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system as described in Section 8.2.1 *Photography of EB Target Wound and Other Wounds*.
- Observation of and, if wished by the patient, assistance in wound dressing change and the application of study medication.
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

After wound dressing change

- The assessment of "procedural" pain as described in Section 9.2.1 *Visit 1 (Site Visit at* D0).
- Study medication will be reviewed. All used and unused medication will be returned and counted. The unused tubes will be redispensed. Additional study medication will be dispensed as required.

9.5.3 Visit 9 (Site Visit at M12±14 Days)

The patient will come in for a site visit at M12±14 days.

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- The assessment of disease severity from both clinician and patient/family perspective using the iscorEB (only when available in the local language) as described in Section 9.4.
- The assessment of health-related quality of life using the EQ-5D instrument as described in Section 9.4.
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents.
- A blood sample will be taken for haematology (full blood count with white blood cell differential), biochemistry panels (Na, K, Ca, Cl, P, BG) including renal (urea, creatinine), and hepatic function tests (serum total protein, albumin, ALT, AST, GGT, and AP). Betulin levels are not required at this visit.

After removal of wound dressings

- The assessment of total body wound burden as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of BSAP of TBSA affected by EB partial thickness wounds as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- Observation of and, if wished by the patient, assistance in wound dressing change and the application of study medication.
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.

After wound dressing change

- Study medication will be reviewed. All used and unused medication will be returned and counted. The unused tubes will be redispensed. Additional study medication will be dispensed as required.

9.5.4 Interim Calls (M6, M9, M15, M18, and M21 [±28 Days])

Interim phone calls will be conducted by the study team at M6±28 days, M9±28 days, M15±28 days, M18±28 days, and M21±28 days to encourage continuous study participation and to conduct safety/tolerability assessments. The patient will also be asked about frequency of wound dressing change, method of study medication application, and type of

dressing used since the last visit/call. If required, patients may be asked to visit the site for further evaluations. A site visit may be scheduled instead of an interim phone call to facilitate dispensing and return of study medication. If the patient attends the site for study medication dispensing, he/she is not required to change wound dressings and apply study medication at the visit.

9.5.5 End of Follow-up Visit 10 (M24±14 Days)/ Premature Discontinuation of Follow-Up Phase

The patient will come in for the EoFU visit at M24±14 days. The EoFU visit should also be performed at any time if the patient is prematurely discontinued from the Open-label Follow-Up Phase of the study.

Before wound dressing change

- The record of AEs and/or SAEs.
- The record of concomitant medication.
- A physical examination will be performed.
- Vital signs such as heart rate, respiratory rate, and body temperature will be recorded.
- ECG.
- The assessment of disease severity from both clinician and patient/family perspective using the iscorEB (only when available in the local language) as described in Section 9.4.
- The assessment of health-related quality of life using the EQ-5D instrument as described in Section 9.4.
- A urine pregnancy test in all women of childbearing potential including postmenarchal female adolescents.
- A blood sample will be taken for haematology (full blood count with white blood cell differential), biochemistry panels (Na, K, Ca, Cl, P, BG) including renal (urea, creatinine), and hepatic function tests (serum total protein, albumin, ALT, AST, GGT, and AP), and betulin levels.

After removal of wound dressings

- The assessment of total body wound burden as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The assessment of BSAP of TBSA affected by EB partial thickness wounds as described in Section 9.2.1 *Visit 1 (Site Visit at D0).*
- The record of frequency of wound dressing change, method of study medication application, and type of dressing used since the last visit.
- All used and unused medication will be returned and counted.

10 COLLECTION, STORAGE, AND SHIPMENT OF LABORATORY SAMPLES

The safety laboratory tests including haematology and biochemistry panels will be performed at the local hospital laboratories. If safety laboratory data within 4 weeks prior to enrolment is available, it should be documented in the eCRF as baseline data.

Amryt Research Ltd. will provide urine pregnancy test strips to the sites for conducting urine pregnancy tests in women of childbearing potential.

Dried blood spots from blood samples will be sent to the central laboratory (Nuvisan GmbH, Germany) for betulin analysis. All samples will be kept for up to 2 years after the study is completed.

If the investigator takes a wound swab for a suspected EB wound infection, the result should be documented in the eCRF.

11 DRUG SAFETY

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or a SAE as provided in Section 11.1 *Definitions*. This includes the evaluation of its seriousness, its severity, and the causal relationship to the investigational product and/or concomitant therapy (see Section 11.2 *Recording of Adverse Events and Serious Adverse Events*).

At each visit, the patient will be asked whether any AEs have occurred. A diagnosis of the event based on signs, symptoms, and/or other clinical information should be established if possible. The diagnosis should be recorded as an AE and/or SAE in the corresponding section of the eCRF rather than the individual symptoms. If no diagnosis is known and neither clinical signs nor symptoms are present, the abnormal finding should be recorded.

The patient should be observed and monitored carefully until the AE has resolved, the condition will have stabilised, or its cause will have been identified completely. The investigator will be responsible to ensure that FU will include any supplemental investigations that may be indicated to elucidate the nature and/or the cause of the event.

11.1 Definitions

The definitions of this section follow the tripartite harmonised International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6 '*Good Clinical Practice (GCP)'* and E2A '*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'*.

11.1.1 Adverse Event

An 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.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

11.1.2 Adverse Drug Reaction

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

All AEs judged by the reporting investigator or the sponsor as having a reasonable causal relationship to the study medication qualify as ADRs.

11.1.3 Unexpected Adverse Drug Reaction

If the nature or severity of the ADR is not consistent with the '*Reference Safety Information'* described in the '*Investigator's Brochure'* (see Section 18.1 *Source Documents*), it is an unexpected ADR.

11.1.4 Serious Adverse Event or Adverse Drug Reaction

Special medical or administrative criteria are needed to define reactions that, either due to their nature ('serious') or due to the significant, unexpected information they provide, justify expedited reporting.

Please refer to Section 11.2.2 *Assessment of Severity* for the difference between the terms 'serious' and 'severe'.

An SAE or serious ADR (SADR) 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

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical and scientific judgement should be exercised in deciding whether an AE is serious in other situations. 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 should also be considered serious.

Serious AEs related to the underlying disease will not be expedited as SAEs for the study medication.

11.1.5 Suspected Unexpected Serious Adverse Reaction

A SUSAR is a suspected adverse reaction related to the study medication that is both unexpected and serious.

The nature or severity of the unexpected ADR is not consistent with the '*Reference Safety Information'* described in the '*Investigator's Brochure'* (see Section 18.1 *Source Documents*).

If the investigator or the Medical Monitor judges an SAE not previously documented in the '*Investigator's Brochure*' (see Section 18.1 *Source Documents*) to be related to study medication, the event will qualify as SUSAR and will be subject to expedited regulatory reporting.

11.1.6 Anticipated Adverse and Serious Adverse Events

Patients participating in this study are suffering from EB, which can be associated with significant multiorgan involvement.

Anticipated Adverse Events

Refer to Appendix 19.2 in Section 19 *Appendices* for an overview of '*anticipated AEs*' by system organ class and lowest level term coded using Version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Anticipated Serious Adverse Events

In EB patients, often in-patient hospitalisation for routine multidisciplinary care is necessary. Hospitalisation per se will not be considered as criterion for expedited reporting except for hospitalisation or prolongation of hospitalisation judged by the investigator to be unanticipated with regard to disease course.

11.2 Recording of Adverse Events and Serious Adverse Events

11.2.1 Assessment of Seriousness

See Section 11.1.4 *Serious Adverse Event or Adverse Drug Reaction* for the definition of SAEs and SADRs.

11.2.2 Assessment of Severity

The severity of AEs will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (see Section 18.1 *Source Documents*).

The terms ‘severe’ and ‘serious’ are not synonymous:

- **Severity:** The term ‘severe’ is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
- **Seriousness:** The term ‘serious’ is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an AE term is not listed in the CTCAE classification, the severity of the event should be assessed as follows:

- **Grade 1 (mild):** The AE is noticeable to the patient but does not interfere with routine activity.
- **Grade 2 (moderate):** The AE interferes with routine activity but responds to symptomatic therapy or rest.
- **Grade 3 (severe):** The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- **Grade 4 (life-threatening):** The patient is at immediate risk of death.
- **Grade 5 (death):** Death related to the AE.

11.2.3 Assessment of Causality

Careful medical judgement is necessary to determine if there is a causal relationship between an AE and the investigational product:

- **Certain:** A clinical event, including laboratory test abnormality occurring in a plausible time relationship to drug administration, which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, using a satisfactory rechallenge procedure if necessary.
- **Probable:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- **Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Unlikely:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration, which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

- **Conditional/Unclassified:** A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
- **Unclassifiable:** A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

11.3 Documenting of Adverse Events and Serious Adverse Events

All information regarding AEs and SAEs, whether reported by the patient/parent/legal guardian or observed by the investigator, must be documented in the patient's medical record and recorded in the AE/SAE section of the eCRF. For SAEs, the paper SAE form in the investigator site file must also be completed (see Section 11.4.1 *Reporting of Serious Adverse Events*).

The investigator is responsible for recording and reporting AEs observed from the first dose of study medication (DBP D0) to the last dose of study medication at M24±14 days.

All AEs occurring during screening (i.e., after obtaining the patient's written consent, but before starting study medication) should be 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.

All patients will be followed-up for AEs/SAEs for up to 30 days after their last dose of study medication or until the AE/SAE resolves, whichever is the earlier. The Medical Monitor can specify a longer period of follow-up to protect the patient's safety.

If an investigator learns of an SAE to be reasonably related to study medication any time after study medication dosing has stopped, he/she should promptly notify the sponsor.

11.4 Immediately Reportable Information

11.4.1 Reporting of Serious Adverse Events

All SAEs should be reported immediately (i.e., within 24 hours of learning that the event meets the definition of an SAE). The investigator should complete the paper SAE report form in the investigator site file, assess the causality and send the initial SAE report within 24 hours to the Pharmacovigilance Department.

Contact details are provided below:

Safety and Pharmacovigilance Department

Fax:	+ 1 877 464 7787
Email:	INCDrugSafety@INCResearch.com

If the SAE is fatal or life-threatening and is considered at least possibly related to the study medication, the completed SAE form should be sent to the Safety and Pharmacovigilance Department immediately.

The minimum information required for the initial SAE report is:

- Patient number
- Description of the event
- Investigational drug information (start date)
- Reporter information

- Causality assessment

If relevant information is missing at the time of the initial SAE report, the reporter should provide it in a follow-up SAE report(s) upon availability. The follow-up report should contain new, updated, or corrected information. It should further describe whether the event has resolved or continues, if and how it was treated including documentation of all supportive actions taken, and whether the blind was broken or not.

11.4.2 Other Reportable Information

If a patient is confirmed to be pregnant during the study or during FU, the continued use of the investigational product must be re-evaluated immediately. Administration of the investigational product should be discontinued unless the investigator decides, following discussion with the sponsor, that the potential benefit to the patient justifies the potential risk to the foetus.

Any pregnancy or fathering of a child, which occurs for up to 30 days within the last application of study medication should immediately be reported within 24 hours of awareness. While not considered an adverse event or serious adverse event, pregnancies require monitoring and follow up. For data analysis purposes pregnancies will be reported as AE in the eCRF. The investigator will be asked to complete a pregnancy report provided in the investigator site file. In addition, the investigator should provide follow-up information regarding the course of the pregnancy in the middle of pregnancy, at the time of the expected date of delivery and at 28 days/ 4 weeks after delivery of newborns for any potential congenital anomalies. Three follow-up attempts should be made to obtain missing information for the pregnancy cases and pregnancy outcome. Spontaneous abortions should always be reported as SAEs. This management is done regardless of whether the patient has discontinued participation in the study.

Pregnancy and pregnancy outcome of female partners of male trial subjects need to be reported in the same way. The Pregnancy Report Form will be used to report the pregnancy information for the partner of a male subject. A pregnancy informed consent form (ICF) and/or a pregnancy partner ICF may be required per regional /local regulation before any collection of information related to pregnant progress and outcome can be performed.

Pregnancy cases will be captured in the safety database; a narrative will be prepared. If the pregnant female's partner is a participant of the clinical trial, the male partner's study subject number and all relevant treatment information should be captured in the case file. For pregnancy case that results in a live birth, the outcome should be captured within the maternal or paternal case. If a serious adverse event is reported for the newborn, including congenital anomalies, a separate child case should be created and parent case should be cross referenced. Pregnancies will be considered finalized once all fields on the pregnancy notification and pregnancy outcome reports are properly completed. If a pregnancy is ongoing or a new pregnancy report is received after database lock, the responsibility for follow-up/processing is transferred to Amryt Research Ltd.

11.5 Independent Data Monitoring Committee

An IDMC will be established to review and evaluate efficacy and safety data during the DBP of the study. The IDMC will consist of independent experts who will not be involved in the study. The safety reviews will be performed blinded and are to ensure safety for participants and to advise for continuation, modification, or discontinuation of individual patients and/or of the study. Following an unblinded interim safety review, the IDMC will be able to confirm if the study can be expanded to allow the inclusion of children with EB to all ages (i.e., ≥ 21 days and <4 years).

The unblinded interim analysis for sample size re-estimation will take place when approximately 50% of patients have completed D45±7. Depending on the results of the sample size re-estimation, the IDMC will recommend to continue with the initial sample size, increase the sample size, or stop the study for futility.

12 STATISTICAL ANALYSIS

12.1 Statistical Methods

The first full statistical analyses of the study will be performed after all data up to the EDBP visit (D90±7) has been entered and cleaned (including AE, local tolerability and concomitant medication data with date of onset until day of EDBP visit [D90±7]), a database lock of these data has been performed and unblinding has been done. The statistical analysis of the FU will be performed after database closure of the FU and will be reported separately. An unblinded interim analysis will also be performed as outlined in Section 12.3.2 *Unblinded Interim Analysis*.

12.1.1 Statistical Hypothesis

This study is a double-blind, randomised, vehicle-controlled design intended to show superiority of Oleogel-S10 versus vehicle.

The primary endpoint analysis will be performed as follows:

The proportions of patients with first complete closure of the EB target wound within 45±7 days based on clinical assessment by the investigator in the Oleogel-S10 and vehicle treatment groups will be compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB subtype and target wound size class.

The final statistical analysis of the primary endpoint will be performed based on the Cui, Hung, Wang (CHW) approach using a weighted statistic (Cui, Hung et al. 1999) (refer to sample size re-estimation plan for details, and also to Section 12.3.2 *Unblinded Interim Analysis*).

12.1.2 Level of Significance, Multiple Comparisons, and Multiplicity

The testing approach of the study is that the primary efficacy endpoint will be tested at the 5% significance level (two-sided). At the final analysis, in case the primary efficacy analysis is statistically significant, the confirmatory testing approach will continue hierarchically (in the order specified in Section 12.3.4) with the statistical testing of the key secondary endpoints at the two-sided 5% significance level.

The analysis of the remaining secondary and open-label endpoints will be considered as non-confirmatory and descriptive only.

If the primary efficacy endpoint is significant the study will claim the superiority of Oleogel-S10 compared to vehicle. If the primary efficacy endpoint does not show significance at the 5% level, then the study will have failed to show the superiority of Oleogel-S10 compared to vehicle.

The CHW weighted statistics for consideration of sample size re-estimation does not require an adjustment of the significance level in case the interim analysis is for sample size re-estimation only and will not allow for early stopping due to early efficacy.

An unblinded interim analysis with a sample size re-estimation will be performed (see Section 12.3.2 *Unblinded Interim Analysis*).

12.1.3 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 test of equality of binomial proportions at the alpha=0.05 level of significance, a total sample size of 182 subjects (91 subjects per arm) will provide 80% power to detect an improvement of 20 percentage points (i.e., a true Oleogel-S10 rate of 47%. A total of 192 patients are 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).

Following the unblinded interim analysis, the IDMC recommended to have a sample increase of 48 patients (24 per arm) to have a total of 230 subjects. A total of 250 patients are planned to be enrolled into the study and treated to account for drop-out patients.

12.2 Definition of Study Populations

The statistical analysis will be based on the following study populations:

- The safety analysis set (SAF) will include all patients treated at least once with study medication. The SAF will be used for all safety analyses. In the SAF, subjects will be analysed based on the treatment that was received (if different from the randomized treatment).
- All patients from the SAF constitute the full analysis set (FAS). The FAS will be used for all efficacy analyses. In the FAS, subjects will be analysed based on the randomized treatment (if different from the received treatment).
- All patients from the FAS will be assigned to a completer analysis set, if they have not discontinued the study early irrespective of the reason for discontinuation.
- Patients who reasonably adhered to all relevant protocol conditions (i.e., who will have met the eligibility criteria and will have received planned study medication) without relevant protocol deviations constitute the per-protocol (PP) analysis set.

The data obtained will be used to check whether the study protocol was adhered to (e.g., inclusion and exclusion criteria, time windows, concomitant medication). Case-by-case decisions regarding exclusions of patients from the PP analysis will be made prior to final unblinding in a blind data review meeting.

Patients who are randomised but not treated, will not be assigned to any of these analysis sets.

Within the SAF, the patients will be analysed ‘as treated’, i.e., the patients will be assigned to the treatment regimen they will be treated with.

Within the FAS and completer analysis set, the patients will be analysed using the intent-to-treat principle, i.e., the patients will be assigned to the treatment regimen to which they have been randomised.

The FAS will be used as primary population for all efficacy analyses. In addition, the primary efficacy endpoints and some secondary endpoints will be analysed using the PP and the completer analysis set, serving as supportive analyses. Safety analyses will be conducted using the SAF.

12.3 Planned Analyses

12.3.1 Demographic Data and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarised in total and by treatment arm by means of summary statistics (number of patients, mean, standard deviation, minimum, median, maximum) for continuous variables and by absolute and

relative frequencies for categorical variables. Baseline characteristics are defined as all results of the examinations performed prior to the first Oleogel-S10 or vehicle administration.

12.3.2 Unblinded Interim Analysis

An unblinded interim analysis will be performed at the time when approximately 50% of patients have completed D45±7. The unblinded interim analysis will include an unblinded sample size re-estimation using the CHW approach and the conditional power will be computed to check for futility (Cui, Hung et al. 1999, Mehta and Pocock 2011).

Depending on the results of the sample size re-estimation, the IDMC may give the following recommendations regarding the sample size and the continuation of the study:

- Initially estimated sample size is sufficient. Do not increase sample size.
- Increase sample size (to not more than 169 evaluable patients per treatment group, which corresponds to an additional 156 evaluable patients)) to provide a statistical power of 80%.
- Stop for futility.

The initial sample size will not be decreased for any reason. Discussion of various potential scenarios and assumptions at the unblinded interim analysis influencing the re-estimation of the sample size will be provided in the 'sample size re-estimation plan'.

12.3.3 Planned Analysis for Primary Endpoint

The confirmatory testing of the primary endpoint will be performed using the CMH test on the FAS. After the unblinded interim analysis, if it is decided that the sample size needs to be increased then the final statistical analysis of the primary endpoint will be performed based on the CHW.

The FAS will be used as primary population for all efficacy analyses. The first complete closure of the target wound within 45±7 days (i.e., at Visit 5 on day 45±7 or at an earlier visit) will be considered as a failure (wound not closed) or as a success (wound closed) based on the clinical assessment of the investigator as recorded in the eCRF.

For the analysis of the primary efficacy endpoint, missing data for patients in the Oleogel-S10 or vehicle group with regard to wound closure will be considered as failures.

The following supportive and sensitivity analyses for primary efficacy will be performed:

- The primary efficacy analysis will be repeated on the PP and the completer analysis set.

- A CMH test on the FAS will be performed to evaluate the first complete wound closure based on the clinical assessment by the investigator and confirmed by a second observation after 7 days [+2 days] at the CCC visit. That is, the first wound closure will only be considered as a success if both the clinical assessment and the second observation assess the wound as closed.

- A Fisher's exact test and Pearson's chi-square test for comparison between treatment groups on the FAS without consideration of any stratification will be performed for the overall difference in proportions of first wound closure as clinically assessed by the investigator within D45±7, and 95% confidence intervals (CIs) for the difference between the proportions will be provided.

- Further potential risk factors will be investigated by a logistic regression model with consideration of EB subtypes, target wound size class, and additional baseline factors on the FAS.

- In a sensitivity analysis, the primary efficacy analysis will be repeated on the FAS by investigating the effect of "worst-case" imputation for missing values: a patient in the Oleogel-S10 group with missing data will be defined as a failure, while a patient in the vehicle group with missing data will be defined as a success.

- If the primary efficacy analysis significantly favours the Oleogel-S10 group, a sensitivity analysis based on multiple imputation (MI) will be conducted using the tipping point approach to assess the departures from missing at random (MAR) to missing not at random (MNAR) assumptions.

For this analysis only monotone missing patterns will be considered, since it is assumed that at the time of database lock only discontinued subjects will have missing values for the primary efficacy assessment. Monotone missing patterns will be imputed with a discriminant function.

The distribution of missing responses in the Oleogel S-10 group will be assumed to be worse than for the vehicle group. Variations in the assumptions for the MI will be examined to adjust the imputed values until the statistical significance is lost (i.e., the p-value is greater than 0.05).

- The CMH test will be repeated with considering 'complete closure' as patient's status exactly on D45±7 instead of the first occurrence of complete closure within D45±7.

- The CMH test, Fisher's exact test and the chi square test without consideration of strata will be repeated on PP and in the subset of completers.

- The primary efficacy analysis using the FAS will be repeated stratified by the type of wound dressing material used (non-adhesive or fatty gauze).

12.3.4 Planned Analyses for Key Secondary Endpoints

After the superiority of the primary efficacy endpoint has been shown at the 5% significance level, the following key secondary (confirmatory) efficacy endpoints will be tested hierarchically to ensure an overall significance level of 5%:

1) Time to first complete closure of the EB target wound as evidenced by clinical assessment until the end of the double-blind phase (EDBP) at 90±7 days of treatment using the non-stratified log-rank test.

The non-stratified log-rank test will be repeated on PP and on the subset of completed patients, also, serving as supportive analyses.

Additionally, the stratified log-rank test with consideration of EB subtypes as strata will be performed on FAS. Further potential risk factors will be investigated by a Cox regression model on FAS with adjusting for EB subtypes, target wound size class, and additional baseline factors.

2) Proportion of patients with first complete closure of the EB target wound within D90±7 based on clinical assessment by the investigator.

This analysis will be performed similarly as the primary endpoint.

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).

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

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).

Maximum severity will be compared between treatments using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

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) at D90±7.

The changes from baseline will be calculated for the overall score as well as for the separate subscores (total activity score and total damage score) and will be analysed using an 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 will be calculated.

For confirmatory testing, only the change from baseline in the overall score will be tested and if significant, the hierarchy will continue 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 will be 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 will test both the 'Itch Man Scale' and the 'Leuven Itch Scale' separately.

All confirmatory testing of the key secondary endpoints will be performed on the FAS

12.3.5 Planned Analyses for Additional Secondary Endpoints

The following additional secondary efficacy endpoints will be analysed on FAS as described below:

- 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 will be analysed in a similar way as the primary endpoint considering the first complete closure of EB target wound at D45±7.
- 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 will be analysed in a similar way as the primary endpoint.
- 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 will be analysed in a similar way as the primary endpoint. A sensitivity analysis will be performed using the assessment of all photographs of EB partial thickness wounds.
- The percentage change from DBP baseline (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 is calculated as ([wound size at visit x – wound size at baseline] / wound size at baseline) *100%. This will be analysed for each visit using analysis of covariance (ANCOVA) including 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 will be calculated. Additionally, treatments will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype (van Elteren test). A sensitivity analysis will be performed using the assessment of all photographs of EB partial thickness wounds.
- The change from baseline (DBP D0) in total body wound burden will be evaluated by clinical assessment using Section I of the EBDASI at D30±7 and D60±7. The changes for each visit from baseline will be calculated for the overall score as well as for the separate subscores (total activity score and total damage score) and will be analysed using an 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 will be calculated.

- The change from baseline (DBP D0) in BSAP of TBSA affected by EB partial thickness wounds will be evaluated by clinical assessment based on the '*Lund and Browder*' chart at D30±7, D60±7, and D90±7, calculated for overall as well as for the individual clinician item domains. Each score will be analysed for each visit using an ANCOVA with treatment group, EB subtype, and target wound size class as fixed effects, and the respective baseline score as a covariate. The 95% CIs for the difference in least squares means between treatment groups will be calculated.
- The change from baseline (DBP D0) in "background" pain will be 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, and D90±7. Treatments will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
- The change from baseline (DBP D0) in "procedural" pain will be 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, and D90±7. Treatments will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
- The change from baseline (DBP D0) in itching will be evaluated using the '*Itch Man Scale*' or the '*Leuven Itch Scale*' before wound dressing changes at D7±2, D30±7 and D60±7. Treatments will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
- The change from baseline (D0) in the impact of wounds on sleep (in patients ≥ 14 years of age) will be evaluated using 11-point Likert scales at D7±2, D30±7, D60±7, and D90±7. This will be analysed 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 will be calculated.
- The number of days missed from school or from work will be evaluated. All days missed form school or from work will be added up for the entire DBP (D0 to D90±7). Treatment groups will be compared descriptively. Baseline data will be summarised; no change from baseline will be calculated.
- The treatment response (in patients ≥ 14 years of age) will be evaluated using the TSQM, Version 9 before wound dressing changes at D7±2, D30±7, D60±7, and D90±7. This will be analysed 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 will be calculated.

In a blind data review meeting prior to final unblinding, the amount of available data regarding photography and PROs will be evaluated for D7±2 to decide if statistical analysis will be performed for that time point.

Safety endpoints will be analysed on the SAF as described below:

- Incidence, severity, and relatedness of AEs: Adverse events will be summarised and provided as data listings. Verbatim terms will be mapped to preferred terms and organ systems using the current MedDRA version. For each preferred term, the number of events as well as frequency counts and percentages will be calculated. Separate analyses will be conducted using severity, seriousness, and relationship to study medication.
- Vital signs and clinical laboratory values (including betulin) will be summarised descriptively. Changes from baseline (DBP D0) to EDBP (D90±7) will be presented. For

clinical laboratory variables, shift tables will be used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.

- Local tolerability as judged by the investigator will be summarised descriptively.

12.3.6 Planned Analyses for Open-label Follow-up Phase Endpoints

Changes from baseline analyses will be performed using the baseline for the DBP (i.e., DBP [D0]) and repeated using the baseline for the open-label FU phase (i.e., FU [D0]/EDBP [D90±7]). Day 0 of the FU is the same day as EDBP (D90±7).

- Incidence, severity, and relatedness of AEs: Adverse events will be summarised and provided as data listings. Verbatim terms will be mapped to preferred terms and organ systems using the current MedDRA version. For each preferred term, the number of events as well as frequency counts and percentages will be calculated. Separate analyses will be conducted using severity, seriousness, and relationship to study medication.
- Vital signs and clinical laboratory values (including betulin) will be summarised descriptively. Changes from DBP baseline (D0) to EoFU at M24±14 days and from FU phase baseline (FU [D0]/EDBP [D90±7]) to EoFU at M24±14 days will be presented. For clinical laboratory variables shift tables will be used to evaluate categorical changes by examining the proportion of patients whose test values are outside the normal ranges.
- Local tolerability as judged by the investigator will be summarised descriptively.
- The proportion of patients with complete closure of the EB target wound at M3±14 days based on clinical assessment by the investigator and blinded evaluation of photographs will be analysed in a similar way as the primary endpoint with treatment group referring to the group in the DBP. A sensitivity analysis will be performed using the assessment of all photographs of EB partial thickness wounds.
- The changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in total body wound burden will be evaluated by clinical assessment using Section I of the EBDASI at M3±14 days, M12±14 days, and at EoFU at M24±14 days. The change from baseline in total body wound burden as well as clinician items domains will be analysed for each visit using an ANCOVA with treatment, EB subtypes, and target wound size class as fixed effect terms and the respective baseline score as covariate. The 95% CIs for the difference in least squares means between treatment groups referring to the group in the DBP will be calculated.
- The changes from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in BSAP of TBSA affected by EB partial thickness wounds will be evaluated by clinical assessment based on the '*Lund and Browder*' chart at M3±14 days, M12±14 days, and at EoFU at M24±14 days. The change from baseline in BSAP as well as clinician items domains will be analysed for each visit using an ANCOVA with treatment, EB subtypes, and target wound size class as fixed effect terms, and the respective baseline value of BSAP or of the item domains as covariate. The 95% CIs for the difference in least squares means between treatment groups referring to the group in the DBP will be calculated.
- The change from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in "background" pain will be 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. Treatment groups referring to the group in the DBP will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
- The change from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in "procedural" pain will be 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. Treatment groups referring to the group in the DBP will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).

- The change from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in itching will be evaluated using the *'Itch Man Scale'* or the *'Leuven Itch Scale'* before wound dressing changes at M3±14 days. Treatment groups referring to the group in the DBP will be compared using a 2-sided Wilcoxon Rank Sum test stratified by EB subtype and target wound size class (van Elteren test).
- The change from baseline (both DBP [D0] and FU [D0]/EDBP [D90±7]) in the impact of wounds on sleep (in patients ≥ 14 years of age) will be evaluated using 11-point Likert scales at M3±14 days. This will be analysed using an ANCOVA with treatment group referring to the group in the DBP 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 will be calculated.
- The number of days missed from school or from work will be evaluated. Days missed from school or from work will be added up for the 14-days preceding M3±14 days. Data for 14-day periods preceding DBP D0, D90±7 and M3±14 days will be compared taking into account the treatment received during the DBP.
- The treatment response (in patients ≥ 14 years of age) will be evaluated using the TSQM, Version 9 before wound dressing changes at M3±14 days. This will be analysed using an ANCOVA with treatment group referring to the group in the DBP 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 will be calculated.
- 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 baseline will be obtained for the clinician and patient total scores only, separately. 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 will be set to "missing". If baseline values are available but one or more assessments are missing after baseline, the changes from baseline will be obtained with the last observation carried forward.
- 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 will be 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 will be set to "missing". If baseline values are available but one or more assessments are missing after baseline, the changes from baseline will be obtained with the last observation carried forward.

12.4 Statistical Criteria for Study Termination

The criteria for early termination of the study due to futility will be described in the 'sample size re-estimation plan.'

12.5 Handling of Missing Data

Care will be taken during the conduct of this study to minimise the amount of missing data. The last observation will be carried forward to visits that are not conducted due to an early discontinuation to allow for analyses on change from/percentage change from baseline endpoints.

With respect to missing data related to the analysis of the primary efficacy endpoint, details on how to handle missing data are described in Section 12.3.3.

Withdrawn patients will not be replaced but will be evaluated according to their last visit. If no assessment is available after start of therapy, the missing data will not be replaced.

12.6 Time Windows

Data as evaluated during regular visits will be analysed in accordance to the respective visit. Time window violations will not be considered, with the exception of analyses using the PP; a blind data review meeting will be performed prior to data base lock and final unblinding of the study and it may be decided to exclude single visits from the PP analyses due to time window violation. For time to event analyses, the exact visit dates and D0 will be taken for calculating the time to event.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Prestudy Documentation

Prior to enrolment of patients at a study site, specific regulatory documents must be available, such as Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval and curricula vitae of investigators and study staff. Amryt Research Ltd. will inform the investigator which documents need to be provided according to the applicable regulatory requirements.

13.2 Monitoring

Amryt Research Ltd. will appoint qualified and appropriately trained persons to monitor the study and the FU. Monitors will periodically contact the site and perform site visits in accordance with applicable regulations, GCP, and Amryt Research Ltd. approved procedures. Study objectives, study design, and enrolment rate will determine the extent, nature, and frequency of site visits.

The monitor will contact the site before start of the study to discuss the protocol and data collection procedures with the site study team members.

During site visits, the monitor will:

- Check and assess the progress of the study
- Review study data collected
- Perform source data verification
- Identify any issues and address their resolution

Aim of the site visits is to verify that:

- The data are authentic, accurate, and complete
- The safety and rights of patients are being protected
- The study is conducted in accordance with the approved protocol (and any subsequent amendment), GCP, and all applicable regulatory requirements

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, the monitor will conduct all activities as indicated in Section 13.4 *Study and Site Closure*.

13.3 Data Management and Processing

Amryt Research Ltd. is responsible for data quality control. Each study site is responsible for the data documentation and for the maintenance of patient files.

13.3.1 Data Collection

The investigator or an authorised delegate from the study staff will have to complete an eCRF for each patient enrolled including patients who discontinue prematurely. If a patient withdraws from the study, the reason should be noted in the eCRF if possible. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

13.3.2 Data Management Procedures

A separate '*Data Management Plan*' will detail data management vendors, systems, and processes.

13.3.3 Data Verification Procedures

Data will be checked systematically according to a prespecified '*Data Validation Plan*' after they will have been entered into the study database. Queries will be created for errors or missing data and clarified by the study monitor at the investigational site.

13.3.4 Coding

A medical doctor will code all AEs and concomitant diseases according to MedDRA and all concomitant or previous medication based on the World Health Organization Drug Dictionary.

13.3.5 Procedures for Analysis of Consistency and Medical Plausibility

A blind data review meeting will be conducted as soon as all data of the study has been entered into the eCRF and the database has been confirmed as 'clean'. After resolution of all remaining queries, the SAP will be finalised and the database will be locked. All changes to the data will be kept in an audit trail.

A separate database will be open for long-term follow-up data and the upload of target wound photographs for the evaluation by blinded experts. This database will be locked as soon as data of the FU has been entered and confirmed as 'clean'.

13.3.6 Data to be Recorded Directly into the Electronic Case Report Form

The eCRF will serve as source document for the following data that will only be recorded for the study:

- Ethnic origin
- Fitzpatrick skin type
- Wound photographs

13.4 Study and Site Closure

Upon completion of the study or premature study (site) closure, the monitor and the investigator will be responsible for

- Return of all study data to Amryt Research Ltd.

- Data clarification and/or resolution
- Accounting, reconciliation, and return of used and unused study medication
- Review of study site records for completeness
- Return of all study specific equipment to Amryt Research Ltd.

Amryt Research Ltd. reserves the right to suspend or prematurely discontinue this study at either a single site or at all sites at any time for any reason. Amryt Research Ltd. will inform the investigator(s), the IECs/IRBs, and the regulatory authorities if the study will be suspended or stopped prematurely.

13.5 Audits and Inspections

Amryt Research Ltd. or its designee may conduct a quality assurance audit of this study to evaluate compliance with the protocol and the principles of GCP. The investigator agrees to allow the auditor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

Regulatory agencies may conduct a regulatory inspection of this study. If a regulatory authority requests an inspection, the investigator must inform Amryt Research Ltd. immediately about this request. The investigator agrees to allow the inspector(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the inspector(s) to discuss findings and any relevant issues.

14 LEGAL AND ETHICAL REQUIREMENTS

This study will be conducted in accordance with the harmonised tripartite ICH Guidelines for GCP and all applicable laws and regulations, including the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 (see Appendix 19.1, Section 19 *Appendices*).

14.1 Regulatory Authority Approval

Documents required for the application of this study will be submitted to the responsible competent authority according to the applicable country-specific laws and regulations. The study will not start until the competent authority authorises the study.

14.2 Independent Ethics Committee/Institutional Review Board

This protocol, any amendments if applicable, any material provided to the patient (such as patient information, informed consent form and patient questionnaires) as well as additional documents, which may be required by national regulations and the IEC/IRB, will be submitted to the competent IEC/IRB for review and approval.

Written approval from the IEC/IRB must be obtained before starting the study, and must be documented in a letter specifying the date on which the IEC/IRB met and granted the approval. The IEC/IRB approval letter must identify all documents approved by listing the study number, study title, study sites/investigators, date and version of study protocol, and date and version of patient information/informed consent form. A list of IEC/IRB members should be attached to the approval letter.

Any subsequent modifications made to the protocol or to any other documents that must be reviewed by the IEC/IRB must also be submitted to the IEC/IRB in accordance with local procedures and regulatory requirements.

14.3 Patient Information and Informed Consent

The investigator will explain the aims, methods, objectives and potential risks and benefits of the study to the patient and will obtain written informed consent from him/her before he/she will initiate any study-specific procedure. The patient will have sufficient time to ask and resolve any questions pertaining to participation in the study, and to consider study participation. In the event that a patient will be unable to read or will only be able to provide verbal informed consent, the patient's legal representative may act on the patient's behalf. For this study in patients less than 18 years, in addition to information sheets and consent/assent forms for patients (according to applicable local regulations), parent/legal guardian information sheets and consent forms will also be prepared.

The investigator will also explain to the patient that he/she will be free to refuse entering the study or to withdraw from it at any time for any reason. Neither the refusal to give consent nor the withdrawal of consent will result in discrimination of the patient, in particular regarding his/her subsequent medical treatment.

The patient will be asked to review, sign, and date the informed consent form. He/she will receive a copy of the signed informed consent form, including the investigator's signature. The investigator will retain the original document.

The eCRF for this study will contain a section for documenting informed patient consent, which needs to be completed appropriately. The consent form will be reviewed and updated, if the risk/benefit assessment changes or if amendments to the protocol affect the patient's participation in the study. All patients (including those already being treated) will be informed about the new information. Patients are only allowed to further participate in the study if they agree to sign the amended form, indicating that they reconsent to participate in the study.

14.4 Data Protection

Medical information about individual patients obtained in the course of this study is confidential and may not be disclosed to third parties, except authorised monitors, auditors, or inspectors. Confidentiality will be ensured by the use of patient numbers for the identification of each patient; these patient numbers will also be used for patient data in the patient files and eCRFs. The investigator should keep a patient enrolment log showing codes, names, and addresses and should maintain documents, e.g., patient's written consent forms, in strict confidence.

14.5 Notification of Primary Care Physician

The investigator should notify the patient's primary care physician of the patient's participation in the study, if applicable and agreed by the patient.

14.6 Investigator Reporting Requirements

The investigator will ensure that site study team members will promptly bring AEs/SAEs to his/her attention. He/she will report all AEs/SAEs as described in Section 11.3 *Documenting of Adverse Events and Serious Adverse Events* and Section 11.4 *Immediately Reportable Information*. The investigator will inform his/her IEC/IRB of any SAE in accordance with the local reporting requirements.

14.7 Record Retention

Upon closure of the study, the investigator/study site will maintain a copy of all study records in a safe and designated location at the study site in accordance with applicable regulatory requirements. Amryt Research Ltd. will inform the investigator/study site of the time for retaining these records to comply with applicable regulatory requirements.

Essential documents as defined in the ICH E6 Guideline of GCP must be retained until:

- 2 years after the last approval of a marketing application in an ICH region
- There are no pending or contemplated marketing applications in an ICH region
- 2 years will have elapsed since the formal discontinuation of clinical development of the investigational product
- Longer if required by the applicable regulatory requirement(s)/the sponsor

Unless other Union law (outside of the EU) requires archiving for a longer period, the sponsor and the investigator will archive the content of the clinical trial master file for at least 25 years after the completion or discontinuation of the study. The medical files of patients will be archived in accordance with local regulations.

15 PROTOCOL AMENDMENTS

All protocol amendments must be submitted to the competent IECs/IRBs and Regulatory Agencies for information and/or approval in accordance with local requirements. If applicable, approval must be awaited before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients.

16 DISCLOSURE OF INFORMATION

All data and records generated during the study except for patient medical records and all inventions discovered in the course of conducting the study, whether patentable, or not, are the sole and exclusive property of Amryt Research Ltd.

The investigator and site study team members will keep strictly confidential any information provided by Amryt Research Ltd. related to this study and all data and records generated in the course of conducting the study. They will not use the information, data or records for any other purpose than conducting the study without prior written approval of Amryt Research Ltd.

Amryt Research Ltd. will prepare an integrated clinical study report in accordance with the harmonised tripartite ICH E3 Guideline '*Structure and Content of Clinical Study Reports'* after completion of the study.

16.1 Publication of Study Findings

Negative and positive results of this study will be presented at scientific meetings and/or will be published in a peer reviewed scientific or medical journal. By signing the clinical study agreement, the investigator agrees that the results of the clinical study may be used for publication.

The first publication or disclosure shall be a complete, joint multicentre publication or disclosure. Authorship will be discussed with all parties involved, depending on such considerations as recruitment. A premature publication or disclosure of partial results is not possible.

The investigator(s) may use the scientific data generated during the study for non-commercial purposes, e.g., for scientific publications of any kind only after prior written consent of Amryt Research Ltd. The investigator(s) will allow Amryt Research Ltd. to review the proposed publication or disclosure prior to submission for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study.

If Amryt Research Ltd. supposes the proposed publication or disclosure to risk Amryt's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed to allow Amryt Research Ltd. to file a patent application.

17 COMPENSATION FOR INJURIES

Insurance coverage for damages emerging from the study and involving study patients treated with the study medication will be provided according to applicable legal requirements. The investigator must inform the patient accordingly and must point out that the patient should seek the investigator's consent before undergoing other medical treatment, whenever possible. The investigator will advise patients that they must inform the investigator immediately of any injury that might have been caused by study participation.

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19 APPENDICES

19.1 Appendix 1: Declaration of Helsinki

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research
Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best-proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal

information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a

non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, poststudy provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific

information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances, the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations, the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best-proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best-proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

And the patients who receive any intervention less effective than the best-proven one, placebo or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best-proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

19.2 Appendix 2: Anticipated Adverse Events by System Organ Class and Lowest Level Term

System Organ Class	Lowest Level Term
Blood and lymphatic system disorders	Anaemia
Cardiac disorders	Cardiac insufficiency
	Cardiomyopathy
	Congenital cardiovascular anomaly
Investigations	Ejection fraction decreased
	Urine analysis abnormal
	Blood calcium abnormal
	Blood phosphate abnormal
	Inflammatory marker increased
	Carnitine decreased
	Total protein low

System Organ Class	Lowest Level Term
	Selenium low
	Iron abnormal not otherwise specified (NOS)
	Thyroid function test abnormal
	Zinc low
	Body mass index decreased
	Oxygen consumption increased
	Loss of weight
	Full blood count abnormal
	Urine electrolytes abnormal
	Abnormal liver function tests
	C-reactive protein abnormal
	Abnormal serum protein electrophoresis
	Urine albumin/creatinine ratio abnormal
	Autoantibody positive (incl. antinuclear antibodies [ANAs], antineutrophil cytoplasmic antibodies [ANCAs], antibasement membrane antibodies)
Gastrointestinal disorders	Ankyloglossia acquired
	Ankyloglossia congenital
	Tooth abnormal
	Gingivitis/periodontitis
	Anal fissure
	Painful defaecation/constipation
	Colitis
	Diarrhoea
	Gastrointestinal bleeding
	Gastroesophageal reflux
	Odynophagia
	Oesophageal mucosal blister
	Oesophageal diverticulitis
	Oesophageal disorder
	Oesophageal pain
Gastrointestinal disorders (continued)	Oesophageal perforation
	Pyloric stenosis
	Tooth lost
	Stricture and stenosis of oesophagus
	Oral mucosa blistering
	Dental decay
	Vomiting
	Dysphagia
	Fatty liver
Eye disorders	Blister on macula of eye
	Blepharitis
	Blindness
	Corneal erosion
	Scleritis with corneal involvement
	Corneal scar
	Ectropion
	Eye dryness
	Eyelid function disorder
	Visual impairment

System Organ Class	Lowest Level Term
	Keratitis
	Keratoconjunctivitis
	Lacrimal duct obstruction
	Symblepharon
Ear and labyrinth disorders	Acquired stenosis of external ear canal
	Hearing loss
	Hearing impaired
Infections and infestations	Otitis externa
	Infection susceptibility increased
	Otitis media
	Gastroenteritis
	Infection respiratory
	Skin infection
	Bacteraemia/sepsis
Endocrine disorders	Delayed puberty
	Pubertal failure
Congenital, familial and genetic disorders	Microstomia
	Finger hypoplasia
	Muscular dystrophy
	Syndactyly/webbing
General disorders and administration site conditions	Application site pain
	Pain
	Pyrexia
	Multiorgan failure
	Loss of energy
General disorders and administration site conditions (continued)	Deformity
	Growth delay
	Asthenia
	Delayed healing of wound
	Healing delayed
	Wound healing delayed
Metabolism and nutrition disorders	Iron deficiency
	Vitamin deficiency
	Appetite lost
	Dehydration
	Malnutrition
Musculoskeletal and connective tissue disorders	Ainhum
	Contracture
	Juvenile idiopathic arthritis
	Limb/hand/foot deformity
	Myasthenia
	Multiple fractures
	Osteopenia
	Osteoporosis
	Mobility decreased
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Basal cell carcinoma
	Epidermoid carcinoma
	Skin cancer
	Squamous cell carcinoma
	Atypical melanocytic hyperplasia (‘EB-nevi’)

System Organ Class	Lowest Level Term
Psychiatric disorders	Sleep disturbance
	Parasomnia
	Depression
	Anxiety
	Phobia
Renal and urinary disorders	Bladder dysfunction
	Bladder hypertrophy
	Dysuria
	Glomerulonephritis
	Nephrotic syndrome
	Hydronephrosis
	Renal failure
	Abnormal kidney function
	Urethral stenosis
	Urinary retention
	Urogenital disorder
	Urogenital infection bacterial
Reproductive system and breast disorders	Sexual dysfunction
Reproductive system and breast disorders (continued)	Sexual problem
	Dyspareunia
	Vaginal inflammation
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain
	Nose bleed
	Bronchitis
	Respiratory distress
	Stridor
Skin and subcutaneous tissue disorders	Alopecia totalis
	Diffuse alopecia
	Nail dystrophy/loss
	Cheilitis
	Keratoderma
	Pruritus
	Rash
	Rash erythematous
	Skin atrophy
	Poikiloderma
Injury, poisoning and procedural complications	Wound
	Wound oozing
	Wound haemorrhage
	Scarring
Vascular disorders	Bleeding
Surgical and medical procedures	Dental treatment
	Dilatation of oesophagus
	Hand operation
	Foot surgery
	Tracheostomy
	Gastrostomy tube insertion
	Iron infusion
	Blood transfusion
	Skin cancer surgery
	IV antibiotic treatment

System Organ Class	Lowest Level Term
	Dressing changes
	Barium meal
	Endoscopy
	Sedation/anaesthesia for imaging/medical procedures