POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	A long-term non-interventional study to assess the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez (**FOSTER)**
PROTOCOL VERSION IDENTIFIER	V3.0
DATE OF LAST VERSION OF PROTOCOL	24 Nov 2023
EU PAS REGISTER NUMBER	To be added after registration
ACTIVE SUBSTANCE	Birch bark extract (ATC: D03AX13)
MEDICINAL PRODUCT(S)	Filsuvez
PRODUCT REFERENCE	EMEA/H/C/005035
PROCEDURE NUMBER	EMEA_H_C_005035_MEA_001
MARKETING AUTHORISATION HOLDER(S) (MAH)	Amryt Pharmaceuticals DAC
JOINT PASS	No

RESEARCH QUESTION AND OBJECTIVES	The research question is: What is the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez in real-world clinical practice? The Primary objective is to estimate the incidence of first skin malignancy during follow-up in patients exposed to Filsuvez.
COUNTRY(-IES) OF STUDY	Austria, France, Germany, Italy, Netherlands, Spain, and United Kingdom (UK). Additional countries may be added, mainly from, but not limited to, the European Economic Area and UK.
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Confidentiality Statement

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2 LIST OF ABBREVIATIONS

AE	Adverse Events
AESI	Adverse events of special interest
BCC	Basal cell carcinoma
CI	Confidence interval
CRO	Contract Research Organization
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
DMP	Data management plan
EAC	Endpoint Adjudication Committee
EB	Epidermolysis bullosa
EBS	Epidermolysis bullosa simplex
eCRF	Electronic case report forms
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practice
HS	Hallopeau-Siemens
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics committee
IRB	Institutional Review Board
IR	Incidence rate
JEB	Junctional epidermolysis bullosa
MAH	Marketing authorisation holder
MM	Malignant melanoma
PASS	Post-authorisation safety study
RDEB	Recessive dystrophic epidermolysis bullosa

SAE	Serious adverse events
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
UK	United Kingdom

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4 ABSTRACT

FULL STUDY TITLE: A LONG-TERM NON-INTERVENTIONAL STUDY TO ASSESS THE INCIDENCE OF SKIN MALIGNANCIES IN PATIENTS WITH DYSTROPHIC AND JUNCTIONAL EPIDERMOLYSIS BULLOSA RECEIVING TREATMENT WITH FILSUVEZ (FOSTER)
PROTOCOL VERSION: V3.0
MAIN AUTHOR: RENÉ CORDTZ (MD, PHD, SENIOR EPIDEMIOLOGIST, IQVIA)

Rationale and background:

Epidermolysis bullosa (EB) is a rare heterogeneous group of genetic skin fragility disorders characterised by blistering and erosions of epithelial surfaces in response to minor trauma or friction. Some forms of EB are associated with greatly increased incidence of aggressive skin and mucosal squamous cell carcinoma (SCC) and additionally, there are reports of other skin malignancies including basal cell carcinoma (BCC) and malignant melanoma (MM) in patients with EB.

Filsuvez gel with a birch bark extract as an active substance was approved by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) in 2022 for the treatment of partial thickness wounds associated with dystrophic EB (DEB) and junctional EB (JEB) in patients 6 months and older.

Amryt is performing this Category 3 post-authorisation safety study (PASS) as an additional pharmacovigilance activity to further evaluate Filsuvez, with a focus on the risk of skin malignancies (identified as an important potential risk).

Research question and objectives:

The research question of the study is:

What is the incidence of skin malignancies in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice?

The objectives are:

Primary Objective:

1. To estimate the incidence of first skin malignancy during follow-up in patients exposed to Filsuvez

Exploratory Objectives:

1. To estimate the incidence of first skin malignancy during follow-up in patients not exposed to Filsuvez
2. To estimate the incidence of each type of first skin malignancy during follow-up in all patients exposed to Filsuvez and by relevant subgroups
3. To estimate the incidence of each type of first skin malignancy during follow-up in all patients not exposed to Filsuvez and by relevant subgroups
4. To estimate the ratio of incidence rates for the first skin malignancy during follow-up between patients exposed and unexposed to Filsuvez
5. To estimate the incidence of all skin malignancies during follow-up (including first and subsequent skin malignancies), by skin malignancy type in all patients exposed to Filsuvez and by relevant subgroups
6. To estimate the incidence of all skin malignancies during follow-up (including first and subsequent skin malignancies), by skin malignancy type in all patients not exposed to Filsuvez and by relevant subgroups
7. To describe demographic and clinical characteristics of all patients exposed to Filsuvez and by relevant subgroups
8. To describe demographic and clinical characteristics of all patients not exposed to Filsuvez and by relevant subgroups
9. To describe patterns of use in all patients exposed to Filsuvez and by relevant subgroups
10. To describe the management of skin malignancies, including intervention and mortality rates, in all patients exposed to Filsuvez and by relevant subgroups
11. To describe the management of skin malignancies, including intervention and mortality rates, in all patients not exposed to Filsuvez and by relevant subgroups

Study design:

This PASS is a non-interventional, multi-country, cohort study based on primary data collection and secondary use of patient registry data. The study will have an approximately 2-year enrolment period, followed by a 5-year follow-up period. However, since EB is a rare disease and skin malignancy a rare event, the enrolment rates will be monitored, and the enrolment and study periods may be modified based on actual enrolment rates and Filsuvez uptake. Data is collected when patients attend their standard care visits, which for most patients is expected to occur approximately annually. For EB registries, data is collected through the usual registration and collection practice of the respective registries.

The DEB and JEB patients will be assessed for exposure to Filsuvez and followed up for occurrence of skin malignancies from the date of study enrolment (index date) to the date of discontinuation (death, discontinuation from site or registry, physician's decision in sites, withdrawal of consent, emigration, lost to follow-up, or end of the study).

Population:

Inclusion criteria

- Patients with a confirmed diagnosis of DEB or JEB and alive during the enrolment period.

Exclusion criteria

- None (*Patients who were previously exposed to Filsuvez during clinical trials or via early access or compassionate programs are eligible to participate in the study*)

Variables and outcomes:
The following variables are included:

- Filsuvez exposure during the study period: start/stop dates, application, reason for discontinuation
- Demographics: date of birth, sex, race/ethnicity
- DEB and JEB diagnosis and disease characteristics: date of diagnosis, subtype
- Wound characteristics: location, characteristics
- Prior diagnosis of skin malignancy: date of diagnosis, skin malignancy type
- Relevant medical history and comorbidities: diagnosis/event/procedure, date
- Skin malignancies during study follow-up: date of diagnosis, type, location, stage
- Interventions for skin malignancy: diagnostic intervention, surgical excision, therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapies), palliative care
- Outcome of skin malignancy: recovered, remission, recurrence, mortality
- End of Study: patient disposition, date of discontinuation, reason for discontinuation

Data sources:
Two types of data sources are planned for this study:

1. Site-based primary data collection:
    - Specialised EB centres
2. Existing EB disease registries:
    - Registro EB (Italy)
    - Dutch EB Registry (Netherlands)

Study size:
Study size estimations were carried out for the primary outcome (first skin malignancy) by varying incidence rates (IR) between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years. With an estimated IR (based on literature reports of skin malignancy in RDEB patients) of 4 events per 100 person-years, for a target margin of error of 0.25 (6.25% of the IR), the estimated target size of 123 Filsuvez-exposed patients with a follow-up contribution of 2 years per patient across all study countries, would be appropriate. For a follow-up of 1 year and 3 years per patient, an estimated sample size of 246 and 82 Filsuvez-exposed patients are required, respectively.

Data analysis:

This study is planned to be descriptive in nature, and no hypothesis testing will be included. For continuous variables, the number of observations, mean, standard deviation, median, first and third quartiles, interquartile range, and range will be presented, as appropriate. For categorical variables, the numbers and percentages of observations for each of the categories will be presented. Numbers and percentages of missing values will be presented.

Primary Endpoint

IRs (per 100 person-years) and cumulative incidence proportions for first skin malignancies will be reported with corresponding 95% confidence intervals. For calculation of follow-up time attribution in Filsuvez-exposed patients, a post-exposure window of 12 month will be used.

Exploratory Endpoints

For first skin malignancies, crude risk ratio and crude rate ratio will be computed. In addition, malignancy characteristics like time to first malignancy will be presented by Kaplan-Meier curves stratified by Filsuvez exposure status, skin malignancy type and by EB subtype.

In analysis for multiple skin malignancy events per individual, crude event rates per 100 person-years with corresponding 95 % confidence intervals will be reported for skin malignancies overall and stratified by type (SCC, BCC, MM) as well as by skin malignancy event type (de-novo and recurrent tumour).

For Filsuvez-unexposed patients, demographic and clinical characteristics will be assessed on the index date. For Filsuvez-exposed, the demographic, clinical characteristics and patterns of Filsuvez use will be assessed on the date of initiating Filsuvez until its discontinuation or end of follow-up, whichever occurs first.

Subgroup analyses will be carried out by EB subtype, age group at index date and their combinations. In addition, variables like EB wound characteristics e.g., wound location, will be used for subgroup analysis for the primary objective, if feasible. Sensitivity and other analyses will be performed to support the primary analysis.

Milestones

- Registration in the European (EU) PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q2 2024
- Anticipated end of data collection: Q2 2031
- Interim reports will be generated every 24 months (2026, 2028, 2030)
- Final report of study results: 2032

5 AMENDMENTS AND UPDATES

VERSION	DATE	CHANGE HISTORY
1.0	15.12.2022	First version
2.0	13.06.2023	Revision according to PRAC comments; Site-based primary data collection component added to the study.
3.0	13.11.2023	Revision according to PRAC comments and administrative changes in study personnel.

6 MILESTONES

The planned dates for key study milestones are:

MILESTONE	PLANNED DATE
Registration in the European (EU) PAS register	Within 30 days after protocol endorsement by European Medicines Agency (EMA)
Anticipated start of data collection	Q2 2024
Anticipated end of data collection	Q2 2031
Interim reports	Generated every 24 months (2026, 2028, 2030)
Final report of study results	2032

7 RATIONALE AND BACKGROUND

7.1. Background

Epidermolysis bullosa (EB) is a rare heterogeneous group of genetic skin fragility disorders characterised by blistering and erosions of epithelial surfaces in response to minor trauma or friction. The most recent classification from 2020 (Has et al., 2020, *Br J Dermatol*) divides EB into 4 major classical types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB. Subclassification based on molecular findings further characterises the EB patients. Junctional epidermolysis bullosa clinical subtypes include JEB severe, JEB intermediate, JEB with pyloric atresia, JEB localised, JEB inversa, JEB late-onset, JEB laryngo-onycho-cutaneous syndrome, and JEB with interstitial lung disease and nephrotic syndrome. Dystrophic epidermolysis bullosa clinical subtypes include autosomal dominant DEB (DDEB) (intermediate, localised, pruriginosa, and self-improving), autosomal recessive DEB (RDEB) (severe, intermediate, inversa, localised, pruriginosa, and self-improving), and dominant and recessive (compound heterozygosity) (DEB, severe) (Has et al., 2020, *Br J Dermatol*).

Some forms of EB, notably severe RDEB, are associated with a greatly increased incidence of aggressive skin and mucosal squamous cell carcinoma (SCC), arising from the late teens onwards with increasing frequency through early to mid-adulthood Bardhan et al., *2020, Nat Rev Dis Primers*). Squamous cell carcinoma is the leading cause of death in this group of patients, with a cumulative risk of death from metastatic SCC of 38.7% by age 35 years rising to 78.7% by age 55 years, with a median survival of 4–5 years after diagnosis of first SCC (Fine et al., *2009, J Am Acad Dermatol*). In addition, there are reports of other skin malignancies including basal cell carcinoma (BCC) and malignant melanoma (MM) in patients with EB. Basal cell carcinoma was reported to occur at a higher rate almost exclusively within the severe EBS population, with a 43.6% cumulative risk by age 55 years (Fine et al., 2009, *J Am Acad Dermatol*). Malignant melanoma was reported to arise in 0.4%, 0.5%, 1.2%, and 2.1% of patients with EB subtype of EBS Weber-Cockayne (EBS localised), EBS-other, DDEB, and RDEB Hallopeau-Siemens (RDEB-HS), respectively. The cumulative risk of MM in RDEB-HS was 2.5% by age 12 (Fine et al., *2009, J Am Acad Dermatol*).

No approved targeted therapy has existed for EB until June 2022, when Filsuvez gel, with birch bark extract as the active substance, received a marketing authorisation from the European Medicines Agency (EMA) for the treatment of partial thickness wounds associated with DEB and JEB in patients 6 months and older (European Medicines Agency [EMA], Summary of Product Characteristics, 2022). This was subsequently followed by a marketing authorisation approval in the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2022. The approvals were based on positive results in the Phase 3 study with a double-blind, randomised, controlled, parallel-group design to compare the efficacy, safety, and tolerability of

Filsuvez versus a vehicle control gel in EB patients (Kern et al., 2019, *Trials*). The study enrolled 223 DEB and JEB patients (n=109 Filsuvez; n=114 control gel) from 49 sites in 26 countries lasting from April 2017 to March 2020. In this pivotal trial, a total of 4 patients experienced SCC of skin, 1 patient in the double-blind Phase and 3 in the open label phase (based on interim safety analysis data) EMA, Risk Management Plan, 2022). The marketing authorisation holder (MAH) categorised 2 of the events of SCC as possibly related in association with Filsuvez therapy due to temporal association.

7.2. Rationale

As part of the post-authorisation development plan for Filsuvez, Amryt agreed to include a post-authorisation safety study (PASS) as an additional pharmacovigilance activity (Category 3 PASS) to further evaluate Filsuvez, with a focus on the risk of skin malignancies (important potential risk). Therefore, Amryt is conducting an observational long-term non-interventional study to assess the safety of Filsuvez in patients with DEB and JEB in real-world clinical practice. A specific outcome on safety will be the assessment of all skin malignancies (SCC, BCC and MM) in DEB and JEB patients receiving treatment with Filsuvez.

In the general population, the risk of skin cancer is inversely correlated with the amount of melanin present in skin. The correlation is weak and not linear, and there are numerous factors that influence the risk of developing skin cancer. The MAH will collect data on race/ethnicity to describe any possible related patterns between race/ethnicity and Filsuvez exposure to help understand the distribution of patient characteristics.

8 RESEARCH QUESTION AND OBJECTIVES

This study is descriptive in nature, and no hypothesis testing is planned.

The research question is:

What is the incidence of skin malignancies in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice?

Primary Objective:

1. To estimate the incidence of first skin malignancy during follow-up in patients exposed to Filsuvez

Exploratory Objectives:

1. To estimate the incidence of first skin malignancy during follow-up in patients not exposed to Filsuvez
2. To estimate the incidence of each type of first skin malignancy during follow-up in all patients exposed to Filsuvez and by relevant subgroups
3. To estimate the incidence of each type of first skin malignancy during follow-up in all patients not exposed to Filsuvez and by relevant subgroups
4. To estimate the ratio of incidence rates for the first skin malignancy during follow-up between patients exposed and unexposed to Filsuvez
5. To estimate the incidence of all skin malignancies during follow-up (including first and subsequent skin malignancies), by skin malignancy type in all patients exposed to Filsuvez and by relevant subgroups
6. To estimate the incidence of all skin malignancies during follow-up (including first and subsequent skin malignancies), by skin malignancy type in all patients not exposed to Filsuvez and by relevant subgroups
7. To describe demographic and clinical characteristics of all patients exposed to Filsuvez and by relevant subgroups
8. To describe demographic and clinical characteristics of all patients not exposed to Filsuvez and by relevant subgroups
9. To describe patterns of use in all patients exposed to Filsuvez and by relevant subgroups
10. To describe the management of skin malignancies, including intervention and mortality rates, in all patients exposed to Filsuvez and by relevant subgroups

11. To describe the management of skin malignancies, including intervention and mortality rates, in all patients not exposed to Filsuvez and by relevant subgroups

9 RESEARCH METHODS

9.1 Study Design

This is an observational, multi-country, non-interventional, cohort study based on primary data collection and secondary use of patient registry data, investigating the long-term safety of Filsuvez in real-world clinical practice. The use of these data sources will enable the collection of patient-level data, including data on Filsuvez exposure, skin malignancies, medical history, and other clinical characteristics.

The study population will include patients with a confirmed diagnosis of DEB and JEB, regardless of Filsuvez use, and aligned with the approved indication for Filsuvez. Patients who were previously exposed to Filsuvez during clinical trials or via early access or compassionate programs are eligible to participate in this study.

There are no protocol–mandated visits or procedures associated with the study. It is anticipated that the frequency of patient visits will differ according to local standard practice and patient need.

An Endpoint Adjudication Committee (EAC) will adjudicate all skin malignancies (SCC, BCC, and MM) identified in the study in both Filsuvez-exposed and unexposed patients. The EAC will not assess causality nor temporal association between Filsuvez exposure and reported skin malignancies. The EAC comprises an independent group of physicians with the appropriate medical background and expertise to adjudicate the events. The study will have an approximately 2-year enrolment period, followed by a 5-year follow-up period (Figure 1), for a total study duration of 7 years. The enrolment period may be modified based on actual enrolment rates to achieve the required sample size.

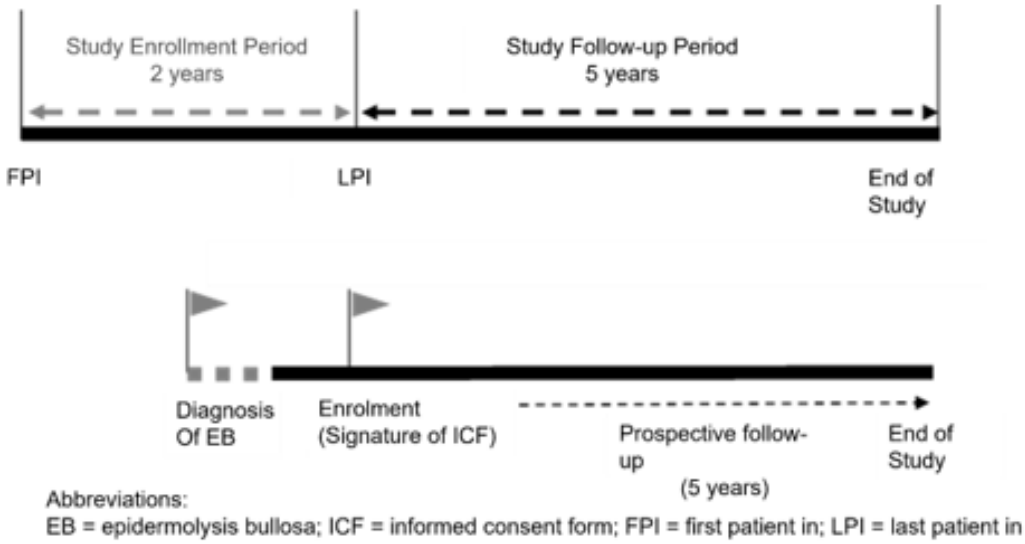

Figure 1: Study design with planned enrolment and follow-up periods.

9.2 Setting

The study plans to enrol approximately 580 patients diagnosed with DEB or JEB from approximately 8 specialist dermatology sites in 5 countries (Austria, France, Germany, Spain, and United Kingdom [UK]), and from 2 existing EB registries (in Italy and Netherlands) with potential for additional sites in these or other countries if required to meet enrolment targets.

9.2.1 Inclusion Criteria

The following inclusion criterium will be applied:

- Patients with a confirmed diagnosis of DEB and JEB, and alive during the enrolment period.

9.2.2 Exclusion Criteria

None (patients who were previously exposed to Filsuvez during clinical trials or via early access or compassionate programs are eligible to participate in this study).

9.2.3 Site-based Approach

Site selection criteria will include the projected availability of eligible patients, the expected use of Filsuvez in routine care, and the ability of the site to collect relevant patient data. Selection criteria and basic site information (e.g., site size, site type) will be collected via a site qualification survey.

Sites will be requested to maintain a patient enrolment log to record the disposition of patients potentially eligible for study participation. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population.

All patients presenting for a routine clinic visit during the enrolment period will be assessed for eligibility, and all eligible patients will be consecutively proposed to be enrolled in the study.

No clinic visits are required as part of participation in this study. All assessments are intended to be performed as part of a routine clinical encounter or by referencing the medical record.

Patients may withdraw consent and discontinue from the study at any time, with no effect on their medical care or access to treatment. If a patient withdraws, the reason for withdrawal should be documented. All information previously collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient. Data that has already been collected, or sent for adjudication, will be retained for use in the analyses.

9.2.4 Registry-based Approach

9.2.4.1 Study Period

The study period will start with the enrolment of the first patient.. The study period will end at the date of final data extraction (analysis cut-off date) in each data source.

9.2.4.2 Enrolment Period

The enrolment period will be the period for patient identification and assessments for study inclusion. The enrolment period is planned to be 2 years. The length of the enrolment period will depend on the number of patients and Filsuvez uptake, and may be extended, as decided by the Study Steering Committee.

9.2.4.3 Index Date

The index date for all patients will be the date of study enrolment.

9.2.4.4 Follow-up Period

Patients will be followed from the date of study enrolment to the date of death, discontinuation from registries, lost to follow-up, or end of study period. The enrolled patients will be allowed for a potential minimum 5 years of follow-up.

9.3 Variables

The variables used in this study are Filsuvez exposure, malignancy outcomes, and relevant covariates. The availability of specific variables may vary across data sources.

9.3.1 Exposure Definition and Measures

This is an observational study of real-world treatment practices in an EB patient population, and this protocol does not recommend the use of any specific treatments. No study medication is provided as part of participation. Treatment with Filsuvez is not required for participation in this study, and patients who are treated with Filsuvez will receive it through routine clinical care.

As a long-term, observational study to evaluate outcomes in patients treated in the post-marketing setting, no restrictions on concomitant treatments are associated with the study. All EB-specific treatments and their start dates will be recorded to take concomitant treatments into consideration.

Patients will be considered unexposed until the date when they start Filsuvez. The exposure to Filsuvez will be determined based on the start of Filsuvez treatment (the records where Filsuvez was prescribed/dispensed/issued/administered depending on available information). Patients will be considered exposed from the treatment start date until treatment end date plus a post-exposure window. For follow-up of first skin malignancy, the post-exposure window is defined as 12-months after the end of Filsuvez treatment.
For the follow-up of all skin malignancies (including first and subsequent skin malignancy events), Filsuvez-exposed patients will be followed until end of follow-up (death, emigration, discontinuation from site/registry, physician's decision, withdrawal of consent, lost to follow-up, or end of study, whichever occurs first) regardless of potential Filsuvez treatment discontinuation.

9.3.2 Outcome Definition and Measures

Any skin malignancy not recorded as recurrent will be considered as de-novo. All malignancies occurring after enrolment will be evaluated by the EAC to confirm the diagnosis.

First skin malignancy: The first occurrence of skin malignancy event during follow-up (ANNEX 3).

First skin malignancy by type (SCC, BCC, MM): The first occurrence of each type of skin malignancy (SCC, BCC and MM) recorded as the first skin malignancy event during follow-up (ANNEX 3).

All skin malignancies: The occurrence of any skin malignancies (including first and subsequent skin malignancies) during follow-up (ANNEX 3).

All skin malignancies by type (SCC, BCC, MM): The occurrence of each type of skin malignancy (SCC, BCC and MM, including first and subsequent skin malignancy events), by de-novo and recurrent malignancies combined and as distinct outcomes, during the follow-up period (ANNEX 3).

Patterns of Filsuvez use

Patients who receive Filsuvez treatment, will be described based on patterns of Filsuvez use:

- Filsuvez application frequency from date of starting treatment and during the (approximately) annual follow-up visits
- Filsuvez application change
- Filsuvez treatment discontinuation (proportion of patients who discontinue Filsuvez, time to Filsuvez discontinuation)

- Reasons for treatment discontinuation during the follow-up

Characteristics and management of the skin malignancy

Among patients who are diagnosed with a skin malignancy during follow-up, the following characteristics will be described (if feasible) in DEB and JEB patients receiving and not receiving Filsuvez treatment:

- Location, type, and staging of skin malignancy
- Date of skin malignancy diagnosis
- Type of diagnostic intervention
- Wound and/or skin characteristics, where malignancy was diagnosed (e.g., wound location and size)
- Filsuvez treatment (yes, no); if yes, treatment location, treatment duration, Filsuvez application frequency (based on dressing change frequency)
- Intervention including surgical excision and/or medical treatment (chemotherapy, radiotherapy and other therapies including immunotherapy, targeted therapies, and palliative care)
- Malignancy outcome (recovered, remission, recurrence, death)
- Patient outcome estimated as death attributed to the skin malignancy

Safety Measures

This study is limited to occurrence of malignancies (SCC, BCC, and MM), which are considered adverse events of special interest (AESI). No other safety data collection is planned.

9.3.3 Covariates

Variables potentially associated with skin malignancies, such as demographics or disease characteristics, will be collected for study participants at the index date, and for patients starting Filsuvez after the index date, these variables will also be collected on the date of starting Filsuvez. For definitions, refer to ANNEX 3.

- Demographic characteristics:
    - Age (derived from date of birth and index date)
    - Sex
    - Race/ethnicity
- Disease characteristics:

  - EB diagnosis (DEB, JEB)
  - Date of EB diagnosis
  - EB subtype (DDEB, RDEB and JEB overall)
  - EB wound characteristics (type and location)
- Comorbidities:
  - Anaemia
  - Malnutrition
- Previous diagnosis of skin malignancy and type of previous skin malignancy
- Other EB-specific treatments (type and start date)

9.4 Data Sources

Two types of data sources are planned to be used in for this study: primary data collection from study sites, and secondary data from pre-existing EB registries. Data sources were selected following the feasibility on data acquisition, data quality, patient numbers, and the possibility of long-term follow-up.

9.4.1 Site-based Data Collection

All data will be extracted from the medical records and during site visits, or collected by the investigator for the purposes of the study. Comprehensive data from patient visits will be entered into eCRFs via an electronic data capture (EDC) system at enrolment and at follow-up time-points, with an estimated 1-2 routine site visits per year.

Assessments collected as part of this study are presented in the Data Collection Flow Chart provided below (Table 1).

Table 1: Study data collection

	ENROLMENT VISIT	FOLLOW-UP VISIT	END OF STUDY
Informed consent	X		
Patient eligibility	X		
Demographics: date of birth, sex, race/ethnicity	X		
DEB and JEB diagnosis and disease characteristics: date of diagnosis, subtype	X		
Wound characteristics: size and location	X	X	X
Relevant medical history and comorbidities, : diagnosis/event/procedure, date	X	X	
Filsuvez treatment: start/stop dates, application, reason for discontinuation	X	X	
Prior diagnosis of skin malignancy: date of diagnosis, type of malignancy, interventions, outcome	X		
Skin malignancies during study follow-up: date of diagnosis, type, location, stage		X	X
Diagnostic interventions in skin malignancy workup		X	X
Interventions for malignancy: surgical excision, therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapies), palliative care		X	X
Outcome of malignancy: recovered, remission, recurrence, mortality		X	X
End of Study: patient disposition, date of discontinuation, reason for discontinuation			X

Abbreviations: DEB, Dystrophic epidermolysis bullosa; JEB, Junctional epidermolysis bullosa.

9.4.2 Registry-based Data Collection

The registry-based data sources will be assessed qualitatively, for presence of variables required for the study and for the ability and willingness to enhance the data

collection for this study (PASS Feasibility Assessment Report: FOSteR EB, Version 1.0, 14 December 2022, for full details of feasibility findings and potential data sources). Therefore, for this study, the already existing secondary anonymised/ pseudonymized data will be collected from registry databases (variables detailed in Table 1). Furthermore, the registry data will be enhanced by the registry holders, if needed, to accommodate the data specification and collection of additional data not routinely collected by the registry. The 2 registries that are planned to be included in this study are described in Table 2.

Table 2: Description of the registries planned to be included in the study

	REGISTRO EB (ITALY)	DUTCH EB REGISTRY (NETHERLANDS)
Year of establishment	2018	1988
Centres description(s)	Two EB specialist multidisciplinary centres	Centre of expertise for EB in Netherlands
Contributing centres	• Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Cà Granda Ospedale Maggiore Policlinico, • Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari	UMC Groningen
Geographical scope	Estimated 50% coverage of all Italian EB patients	National
Number of DEB or JEB patients in registry	71	192
Variables collected	• Demographic variables: age, sex, ethnicity • Disease characteristics: EB type and subtype, diagnosis date • Medical history: baseline comorbidities, previous skin malignancies • Skin malignancy variables: type, grade, stage, location, treatment • SoC treatments: topical/ oral medications, start /end dates • Frequency of dressing changes • Date of death	• Demographic variables: age, sex, ethnicity • Disease characteristics: EB type and subtype, diagnosis date • Medical history: baseline comorbidities, previous skin malignancies • Skin malignancy variables: type, diagnosis date, location • Date of death
Data quality	The registry contains a unique identifier to avoid duplication of records. Data entry is validated by specialist clinicians. Most variables are highly structured with definitions agreed by clinicians. Guided input is provided for data entry.	Patients are pseudonymized and connected via a unique identifier to their electronic medical record. Data is validated by clinical staff, researchers and PI. Data entry has 2-stage process of entry and checking. Some variables are defined (e.g., diagnosis date is always a date of molecular diagnosis) to assure data consistency.

Abbreviations: EB- Epidermolysis bullosa, UMC - University Medical Centre, PI – Principal Investigator, DEB-Dystrophic epidermolysis bullosa, JEB - Junctional epidermolysis bullosa

9.5 Study Size

As the main analysis for the primary outcome (i.e., incidence of first malignancy) is descriptive in nature, the sample size calculation was done to ensure sufficient precision in outcomes based on the half-width of the 95% confidence interval (CI). The background IR was derived from literature, and then sample size estimations were carried out by varying incidence rates (IR) between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years.

Using the estimated background IR (as described below) of 4 events per 100 person-years, with a target margin of error of 0.25 (6.25% of the IR), the estimated minimum study size of 123 Filsuvez-exposed patients with a follow-up contribution of 2 years per patient across all study countries, would be appropriate. For a follow-up of 1 year and 3 years per patient, an estimated sample size of 246 and 82 Filsuvez-exposed patients are required, respectively. The same assumptions can be applied to the unexposed cohort (Table 3), meaning an equal number of Filsuvez unexposed patients is estimated to be suitable in these analyses.

Based on the feasibility assessment, there are approximately 260 patients with EB in registries, and 320 patients at the 8 identified EB-specialised sites. From the feasibility assessments, it is expected that the number of Filsuvez unexposed patients will be at least 240.

Background Rates

Cumulative risks of developing a first SCC by age group and by each of the 3 major RDEB subtypes (generalised severe, generalised intermediate and inverse) have been reported in the literature (Fine et al., 2009, *J Am Acad Dermatolt*). These cumulative risks were then used to derive background incidence rates (IR) for each age group. An assumption used for this calculation was that the risk of developing SCC would increase linearly within each 5-year age groups.

The probabilities of developing a first SCC over a 5-year period have been obtained by age group (from 15-year-old to 30-year-old) and by each of the 3 major RDEB subtypes, by subtracting the cumulative risk of an age group from the cumulative risk of the following age group. For example, from the literature above, the cumulative risk of developing SCC by age 25 was 26.73% and by age 20 was 7.45%, then the probability of developing SCC between ages 20 and 25 was calculated as (26.73% - 7.45% = 19.28%).

These probabilities were assumed to correspond to the number of events observed in 100 patients over the 5-year period. Every patient who did not develop a first SCC was assumed to contribute 5 person-years, whereas every patient who developed a first SCC was assumed to contribute 2.5 person-years.

To obtain an overall IR of RDEB patients for each age group, average of the numbers of events and person-years have been calculated, weighted by the percentages of patients in each of the RDEB subtypes (EMA, Summary of Product Characteristics, 2022), relative to the total number of RDEB patients: 70.9% of RDEB generalised severe, 22.3% of RDEB generalised intermediate, and 6.9% of RDEB inverse (the percentage of RDEB inverse was assumed to correspond to the remaining RDEB patients).

The following reference IR values (per 100 person-years) were obtained with this approach: 1.22 for 15-year-old, 3.35 for 20-year-old, 4.31 for 25-year-old, and 2.67 for 30-year-old.

Parameters Used

Minimum sample size required to achieve a margin-of-error (half of the CI width) for the confidence level for a range of IRs of interest were calculated. This sample size estimation was based on the approach described in World Health Organisation (WHO)'s Cancer Epidemiology: Principles and Methods.

Table 3 shows the minimum required sample size to estimate IRs between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years.

Table 3: Minimum required sample size to estimate an incidence rate with a certain margin of error and estimated follow-up

~3 YEARS OF FOLLOW-UP CONTRIBUTION PER PATIENT									
	Margin of error (per 100 person-years)								
Incidence rate (per 100 person-years)	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.45**	**0.50**
1	129	57	33	21	15	11	9	7	6
2	257	114	65	41	29	21	17	13	11
3	385	171	97	62	43	32	25	19	16
4	513	228	129	**82**	57	42	33	26	21
5	641	285	161	103	72	53	41	32	26
7	897	399	225	144	100	74	57	45	36
10	1,281	570	321	205	143	105	81	64	52
~2 YEARS OF FOLLOW-UP CONTRIBUTION PER PATIENT									
	Margin of error (per 100 person-years)								
Incidence rate (per 100 person-years)	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.45**	**0.50**
1	193	86	49	31	22	16	13	10	8
2	385	171	97	62	43	32	25	19	16
3	577	257	145	93	65	48	37	29	24
4	769	342	193	**123**	86	63	49	38	31
5	961	427	241	154	107	79	61	48	39
7	1,345	598	337	216	150	110	85	67	54

10	1,921	854	481	308	214	157	121	95	77
~1 YEAR OF FOLLOW-UP CONTRIBUTION PER PATIENT									
	Margin of error (per 100 person-years)								
Incidence rate (per 100 person-years)	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.45**	**0.50**
1	385	171	97	62	43	32	25	19	16
2	769	342	193	123	86	63	49	38	31
3	1,153	513	289	185	129	95	73	57	47
4	1,537	683	385	**246**	171	126	97	76	62
5	1,921	854	481	308	214	157	121	95	77
7	2,690	1,196	673	431	299	220	169	133	108
10	3,842	1,708	961	615	427	314	241	190	154

9.6 Data Management

All details regarding site and registry-based data collection processes for data management will be described in the Data Management Plan (DMP).

In both site and registry-based data sources, the data collection will be performed according to a predefined data specification file and a DMP.. Data will also be harmonised and standardized as appropriate using a common data model applied to registry-based and site-based data collection. Security processes will be in place to ensure the safety of all systems and data. The data is stored in a secured restricted area, and it cannot be accessed by anyone except authorised study staff. Appropriate data storage and archiving procedures will be followed. Standard procedures will be in place to restore files in the event of a hardware or software failure. The study may be inspected by Amryt and their affiliates' independent representative(s), scientific committee, or by the competent authorities.

Brief details regarding site and registry-based collection are described below.

9.6.1 Site-based Data Collection

A DMP will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

The eCRFs and any corrections must be documented in the EDC system's audit trail, containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry, and the corrected entry. By signing the affirmation statement/ casebook the investigator confirms that the information in the eCRF is complete and correct. If corrections are made by the investigator's authorised staff after the date of signature on the affirmation statement/casebook, the investigator must again sign this.

Data should be entered in the eCRF in a timely manner and should be consistent with the relevant source document. The eCRF will be designed to collect consistent data and minimize the effect of heterogeneity in reporting within patients' medical charts between sites. High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis.

Every effort will be made to harmonise data collection across different sites by providing clear guidance for data abstraction All clinical data will be processed and stored in a database, and all data collected will be stored in accordance with local laws and regulations.

9.6.2 Registry-based Data Collection

The data management processes differ by country and data source. The data collection will be done on approximately an annual basis, starting with the baseline and enrolment visit at the time of enrolment and continuing throughout the entire follow-up period, including retrospective data collection to the time of initiation of Filsuvez early access program or compassionate use or when commercial Filsuvez was initiated. Data collection is primarily based on the data extraction of medical records from all standard care visits including scheduled and/or unscheduled throughout the entire follow-up period. In addition, registry-based data enhancement

will be conducted to capture additional variables needed for this study but not routinely collected by the registries. This data enhancement may be implemented by registries developing or adapting their own eCRFs considering the data specification.

All data used in this study will be in the form of electronic records, and the data holders collect and manage data according to their own standards. The study data from each data source will be extracted and this extraction will be conducted by the individual data source holders. After data are extracted, the data holders will make data accessible for analysis. All individual-level data will have original personal identifiers replaced with a study identification number and no identifiable personal health information will be transferred.

The data providers conducting the data management and statistical analysis for the study will store the datasets and analytic scripts according to the data provider's procedures. Full audit trail starting from raw data obtained from registry holders/sites and ending to with statistical tables and graphs in reports will be maintained. Source code of data management and data analyses will be kept for inspection for 5 years after publication of results.

9.7 Data Analysis

9.7.1 General Considerations

This study is purely descriptive, i.e., does not include any statistical testing of outcomes between Filsuvez-exposed and unexposed patients. The following sections describe the analyses that will be carried out in this study. Data analyses will be stratified as described in Section 8 and Section 9.7.2.2, depending on data availability and patient counts. Demographic, clinical characteristics, Filsuvez use patterns, and characteristics of skin malignancies will be included in the descriptive analyses of the Filsuvez-exposed and unexposed patients. Continuous variables will be described using mean, standard deviation, median, first and third quartiles, interquartile range, range, as appropriate. Categorical variables will be described with counts and percentages (relative to the number of non-missing observations for each variable).

Analyses are planned to be carried out in pooled individual-level data (only if feasible) from all data sources involved in the study. Otherwise, analyses will be based on aggregate-level data obtained per data source. Data will be harmonised and standardized as appropriate using a common data model. All statistical analyses to create tabulations and graphics, creation of analysis database, will be performed using statistical software (SAS version 9.4 or later, or R [version 3.5.0 or later]), whichever feasible.

A full description of the analytical approach, data derivations, category definitions, analyses and presentation of the study results will be detailed in the Statistical analysis plan (SAP).

9.7.2 Planned Analyses

Crude IRs and crude cumulative incidence proportions will be calculated by overall and subgroups for both Filsuvez-exposed and unexposed patients. The person-time of each patient for IR calculation will be based on the follow-up and censoring criteria presented in the below subsection on follow-up period and person-time attribution. For the calculation of the crude IRs, denominator will be the pooled person-time of all patients within each exposed and non-exposed group and numerator will be the pooled number of occurrences of any first skin malignancy overall or by type (SCC, BCC and MM). Crude IRs will be presented per 100 person-years with 95% CI.

With a focus on long-term safety events, the crude cumulative incidence proportion during person-time exposed to Filsuvez and time unexposed will be calculated. Crude cumulative incidence will be quantified for 1-year, 2-year, 3-year, 4-year and 5-year intervals cumulatively. For the person-time unexposed, the denominator is defined as the patient population initially at risk on index date as the estimates are cumulative. For the person-time exposed to Filsuvez, the denominator is defined as the population observed to start Filsuvez. The numerator will be comprised of counts of incident events during the person-time as defined in Section 9.7.2.1 recorded during each cumulative interval and summed to reflect the cumulative count for the interval. The crude cumulative incidence proportion will be calculated according to the formula:

$$\frac{\textit{Total number of patients on Rx with first event during cumulative interval of interest}}{\textit{Population initially at risk}} * 100$$

In addition, plots of cumulative incidence function will also be presented, calculated using the Nelson-Aalen non-parametric method, over the study period for occurrences of any first skin malignancy (SCC, BCC and MM) under consideration. Cumulative incidence function plots will be presented with a 95% CI.

To describe malignancy characteristics, time to first malignancy will be presented by Kaplan-Meier curves stratified by Filsuvez exposure status, skin malignancy type and by EB subtype.

The crude ratios of the incidence and risk for occurrences of any first skin malignancy (overall and by type of malignancy: SCC, BCC and MM) with 95% CIs will be calculated between Filsuvez-exposed and unexposed patients.

For the analyses considering all skin malignancies (first and subsequent events), event rates with respective 95% CI will be calculated for Filsuvez-exposed and unexposed patients by dividing the total number of skin malignancy events (first and subsequent events irrespective of type, and by type of malignancies: SCC, BCC and MM) by the total person-years at risk.

Patterns of Filsuvez use, as defined in Section 9.3.2, will be assessed using the information collected during exposure to Filsuvez. For the analysis of time from the initiation of Filsuvez therapy to its discontinuation, Kaplan-Meier curves will be reported, along with median days on treatment and the corresponding 2-sided 95% CI.

Mortality rates per 100 person-years (with 95% CI) will be calculated for patients with any skin malignancy and for patients with each type of skin malignancy per cohort. The denominator will be the pooled person-time of all contributing patients within the specific group of patients with skin malignancy. The person-time of each patient will be based on the follow-up criteria presented in Section 9.7.2.1. The numerator will be the number of deceased patients within the specific cohort whose death is attributable to any skin malignancy or to each type of skin malignancy, as appropriate.

9.7.2.1 Follow-up Period for Person-time Attribution

The follow-up period in analyses of first skin malignancies for Filsuvez-unexposed patients will be from the index date until date of the first skin malignancy, censoring, start of Filsuvez, or the end of the study, whichever occurs first. The follow-up period for Filsuvez-exposed patients will be from the treatment start date until date of the first skin malignancy, end of 12-month post-exposure window in case of treatment discontinuation, censoring, or the end of the study, whichever occurs first.

The follow-up period in analyses of all skin malignancies including both first and subsequent registered skin malignancies, will be from the index date for Filsuvez-unexposed patient, and from Filsuvez treatment start date for exposed patients, until the date of censoring, Filsuvez treatment start in unexposed patients, or the end of the study, whichever occurs first.

For person-time attribution in exposed patients, after stopping Filsuvez treatment and following the post-exposure window, patients will not be considered unexposed again, i.e., they cannot contribute with person-years of observation to the unexposed group once exposed to Filsuvez.

Figure 2 shows hypothetical scenarios of person-time attribution to each exposure group during the follow-up period.

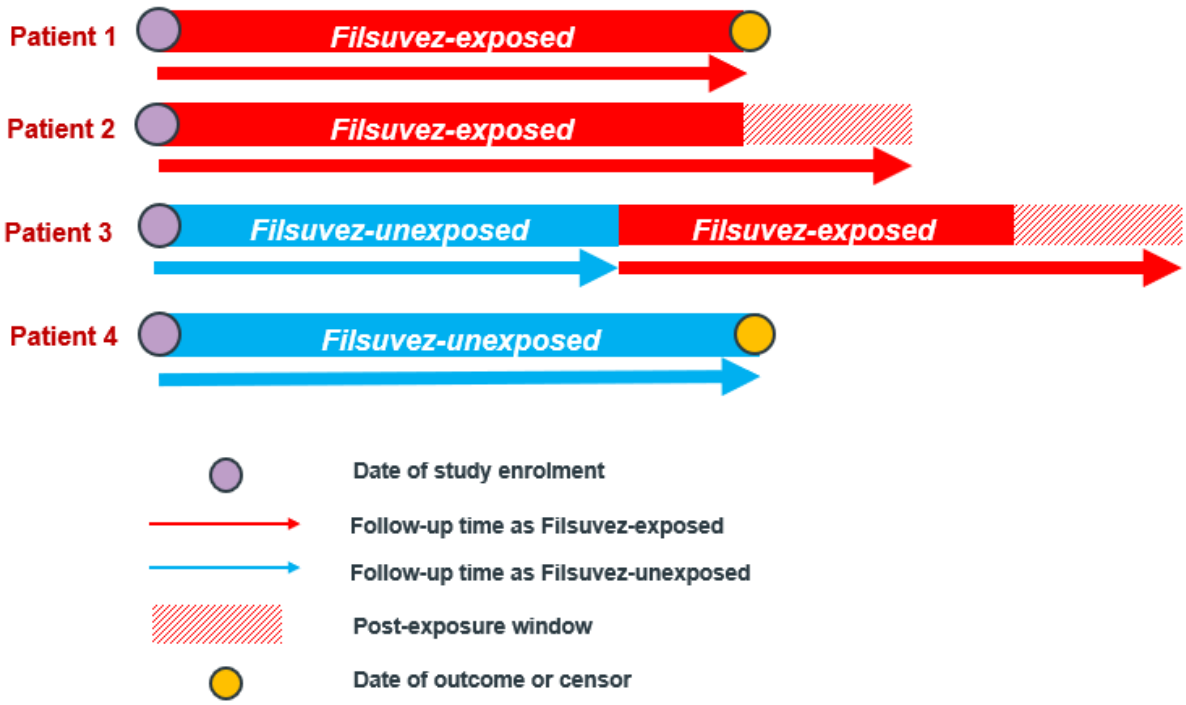

Figure 2: Definition of exposure to Filsuvez in DEB and JEB patients in the study population

9.7.2.2 Subgroup Analyses

The categories of each variable used in the subgroup analyses are listed below:

- EB subtype: DEB (DDEB, RDEB) and JEB
- Age at index date (2 types of stratification):
    - Patients <10 years and ≥10 years
    - Patients <10 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years and ≥60 years

  Age categories may be collapsed if the number of observations in any category is considered insufficient and will be described in the SAP. Data analyses will

be additionally stratified by combinations of age category and EB subtype (if sample size permits).

- EB wound characteristics (if feasible)

9.7.2.3 Sensitivity Analyses

The following sensitivity analyses will be considered for primary objective and exploratory objectives 1, 2 and 3 using available data:

1. Calculation of crude IR and cumulative incidence proportion excluding those with skin malignancy history to remove all malignancies that could be attributed to recurrence.

2. Analysis where Filsuvez-exposed patients who discontinue treatment will be considered as exposed till end of follow-up, i.e., no limit on post-exposure window to capture the long-term effects of Filsuvez.

3. Analysis applying a 6-month post-exposure window instead of 12 months.

4. Analysis considering all patients that commence treatment with another EB-specific treatment will be censored on the date of starting that treatment.

5. Analyses of sampling Filsuvez-unexposed patients by age: Analyses considering creating balanced sub-cohorts (exposed & unexposed) with regards to the age of Filsuvez-exposed patients at treatment initiation. Below are the salient points for this approach:

    - For each Filsuvez-exposed patient, the age at Filsuvez treatment initiation will be calculated.

    - From unexposed patients with similar age interval (+/- 1 year, with a potential incremental change of 1 year up to 5 years for Filsuvez-exposed patients that cannot be assigned a sampled patient), one unexposed individual will be randomly sampled.

    - To be eligible for sampling, the unexposed individual has to be enrolled into the study on or prior to the date when they reached the attained age of the Filsuvez-exposed patient to whom they potentially are sampled.

    - The final result will be calculated from the sub-cohorts of exposed and unexposed individuals, such that the age at treatment initiation

distribution in the Filsuvez treated patients will be similar to the age at the aligned start of follow-up in Filsuvez-unexposed sampled patients.

- In this analysis, Filsuvez-exposed time will be calculated in the same manner as in the primary objective, i.e., follow-up from treatment start date to treatment end date plus 12-month post-exposure window. However, for the sampled Filsuvez-unexposed patients, follow-up will start from the date when they reached the attained age of the Filsuvez-exposed patients to whom they were sampled, and this date may be different than the index date (Figure 3).

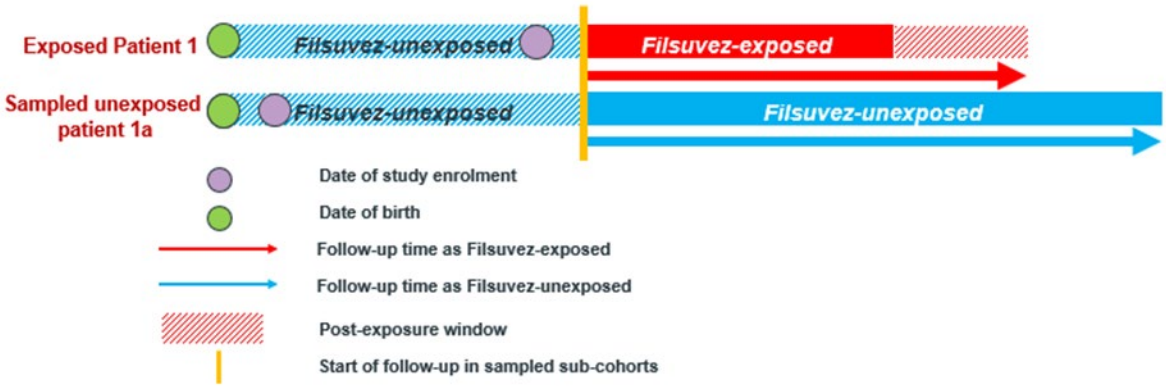

Figure 3: Follow-up time attribution for the occurrence of the first skin malignancy in sensitivity analysis 5

Additional details on the sensitivity analyses will be described in SAP.

9.7.3 Handling of Missing Data

For the current study, feasibility has been performed and variables of interest are expected to be available in routine care..

Should missing data occur, methods commonly used in non-interventional studies for handling missing data will be applied. The number of patients with missing data will be reported for each variable in the study. For the descriptive tables, missing data will be described separately and not included in the denominator for the calculation of the percentage for each category of a particular variable. Full details on handling of missing data will be described in detail in the SAP.

9.8 Quality Control

The study is designed according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11, July 2023) and the ENCePP Checklist for Study Protocol.

9.8.1 Site-based Data Sources

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Remote and on-site site monitoring will be performed to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Amryt's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.8.2 Registry-based Data Sources

Standard procedures will be used to ensure data quality and integrity, including quality checks described in Section 9.6. Data specification files will be used to ensure accuracy and consistency in data collection. To minimize the risk of inaccurate information, all retrieved data will undergo quality check for possible inconsistences or implausible information. The data holders will be queried in case of inconsistencies.

9.9 Limitations of Research Methods

Selection bias

The EB registries and specialised EB centres involved in this study are selected considering feasibility (sample size, ability to enhance or collect data, data quality,

etc.). There is a risk that the rates of skin malignancies for EB patients from the registries and EB sites cannot be generalised to include DEB and JEB patients not followed in such specialised care. Participating physicians at study sites are expected to invite all eligible patients to participate, and the enrolment period will be long enough to ensure the enrolment of less severe patients that are seen less frequently by sites, and thereby minimize selection bias.

Considering the difficulties of patient enrolment in such a rare disease as EB, this study will include both prevalent and newly diagnosed patients. The prevalent patients survived long enough to be included in the study and may have less severe disease than the overall DEB and JEB patients, which could result in selection bias. Further, by including patients with prevalent EB and starting follow-up potentially years after their diagnosis, this will impact the assessment of the rate of skin malignancies in a Filsuvez-unexposed EB cohort.

Most patients will be identified after Filsuvez received market authorisation. It is likely that patients included in the study who were exposed to Filsuvez during the pre-authorisation period (clinical trials, early access program, or compassionate use program) and patients enrolled during the early study period may be different from those included during the later years in terms of clinical characteristics since Filsuvez may be more widely prescribed following market launch, with easier and wider access. Such patterns of uptake occur in most new drugs, and the likely impact on this study is expected to be minimal.

Information bias

Data specification files and unified eCRFs will be used to ensure accuracy and consistency in data collection. Some heterogeneity in data collection is likely to exist due to differences in the data collection by the registries and practical feasibility in data sources. To minimize the risk of inaccurate information, all retrieved data will undergo quality check for possible inconsistences or implausible information.

Informative censoring might exist because of the disease latency period for skin malignancies, and the 12-month post-exposure window may be not adequate to capture cancer development. To explore the impact from such bias, sensitivity analyses considering different latency periods (post-exposure window extended to end of patient follow-up and a 6-month post-exposure window, respectively) will be conducted.

In this study there is no lag-period applied to the Filsuvez exposure definition. Thus, protopathic bias could affect the IR estimates of the exposed patients. However, because EB patients are a high-risk population with regards to skin malignancy, and because of the unknown effect of Filsuvez, if any, in terms of the pathogenesis of skin malignancies in EB, it is difficult to decide an appropriate lag-period.

Confounding

The characteristics of DEB and JEB patients receiving Filsuvez are likely to differ compared to those not receiving Filsuvez. Decisions on treatment initiation may be influenced by different factors (e.g., disease severity, clinical presentation or EB subtype), which may be associated with the risk of occurrence of study outcome and lead to confounding by indication.

However, existing disease severity indices have mainly been used in clinical trials and are not consistently or routinely recorded in clinical practice nor are they well captured in registries. The feedback from the feasibility assessment and discussions with potential sites was that disease severity is not routinely captured at the majority of these; and those that do record it, do not consistently use the same severity index. Instead, EB diagnosis as well as subtype, EB-related conditions as anaemia and malnutrition, and history of skin malignancy could be considered relevant proxies for EB severity; and these characteristics are presented for Filsuvez exposed and unexposed patients. Further, the incidence of skin malignancy will be presented by EB subtype to facilitate the interpretation of results in the context of the different disease severity between the subtypes.

The incidence rate ratios and risk ratios may be confounded. Subgroup analyses by key confounding variables will be conducted, thus providing a descriptive measure of the size and direction for these confounding variables and making the interpretation and informal comparison between groups more straightforward. Statistical modelling to control for confounding is not considered feasible in this study due to the limited sample size for the rare disease and the unavailability of important relevant variables, e.g., disease severity.

There are no curative therapies with DEB and JEB, no established treatment lines, and a variety of topical products (skin cleansing additives, antimicrobials and emollients) are used among patients (Shayegan et al., 2020, *Pediatr Dermatol*). There might be differential use of treatments between Filsuvez-exposed and the unexposed patients, and the heterogeneity of treatments need to be taken into account when interpreting the results.

The occurrence of skin malignancy increases with age and, by design, the exposure to Filsuvez will occur chronologically after the unexposed period for patients in this study. In an attempt to account for this, sensitivity analysis 5 will be carried out. Using a sampling approach on the unexposed patients, the start of follow-up will be aligned on attained age to ensure more balanced age distribution between Filsuvez-exposed and unexposed patients (Section 9.7.2.3).

9.10 Other Aspects

An Independent Study Steering Committee will review study data periodically and make recommendations to the sponsor regarding the study conduct, as well as assist in study execution, interpretation, publication planning, and manuscript review.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Overarching Principles for the Conduct of the PASS

The principles outlined in this subsection apply to both the site- and registry-based data collection approaches. To ensure the quality and integrity of research, the study is conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and its amendments (World Medical Association, 2013) and follows the principles of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (ICH GCP, 2016), Good Epidemiological Practice (Hoffmann et al., 2019, E*ur J Epidemiol*), Good Pharmacovigilance Practices (GVPs), Guidelines for Good Pharmacoepidemiology Practices (GPPs) by the International Society for Pharmacoepidemiology (ISPE), applicable regulatory requirements (Public Policy Committee ISoP, 2016, *Pharmacoepidemiol Drug Saf*) and General Data Protection Regulatory (European Union. REGULATION (EU) GDPR, 2016). Competent Authority and Institutional Review Board (IRB) /Ethics committee approval or notification will be obtained prior to the initiation of the study as necessary per local regulation.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). The investigator will ensure that the patients' anonymity is maintained. Only authorised persons will have access to identifiable personal details, if required for data verification.

10.2 Site-based Data Collection

10.2.1 Patient Information and Informed Consent

Where required, an Informed Consent Form (ICF) must be signed by the patient, and/or assent by minors whose parents/legal representatives provide consent, before his or her participation in the study. Legal representative consent/minor assent is applicable to this study because the study population includes children who might still not be able to consent at the time of this study; if a patient is not of legal age, then the patient's assent must also be obtained according to local requirements. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. If applicable, it will be provided in a certified translation of the local

language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

10.2.2 Patient Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. The patient identifier obtained from EDC at enrolment will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the study countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of ICH GCP E6 guideline (revision 2) regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

10.2.3 Independent Ethics Committee (IEC)

This study may require review and approval by Ethics Committees as per local requirements. The prescribing physicians participating in this study must ensure that the required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation at the site. In accordance with local regulations, patients will be required to provide written consent before enrolment into the study, prescribing physicians participating in the study must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are

clearly and fully informed about the purpose of the study, potential risks, and the patient's rights and responsibilities when participating in this study. Consistent with local regulations and prior to enrolment of patients at a given site, the study protocol will be submitted together with its associated documents (eg, ICF) to the responsible IRB/IEC for its review. Patient enrolment will not start at any site before Amryt has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

10.3 Registry-based Data Collection

For secondary use of registry-based data, review and approval by Ethics Committees may also be required as per local regulations. The ethical approval will be applied as necessary in each registry, and consent will be obtained from patients when required for their data to be used in this study.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

The only safety data being collected as part of this study relates to skin malignancies, which will be collected for all patients and centrally adjudicated. Skin malignancies will be considered Adverse Events of Special Interest (AESI) for the purpose of this study. There is no other formal safety data collection as part of this study. Participating physicians are reminded to report any safety events through standard reporting procedures of routine pharmacovigilance.

11.1 Definitions

Adverse Events (AEs) An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. Pre-existing conditions that worsen during a study are to be reported as AEs.

If, according to the investigator, there is a worsening of a medical condition that was present prior to the administration of the intervention, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the intervention that remains unchanged or improved should not be recorded as an AE at subsequent visits.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to product, action(s) taken, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

Serious Adverse Events (SAEs)

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE must fulfil at least one of the following criteria at any dose level:

- Results in death
- Is life-threatening as it occurred
- Patient was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Defined as a substantial disruption of a patient's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Constitutes an important medical event

Based upon appropriate medical judgment, event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Event Severity

Event severity is defined as a qualitative assessment of the degree of intensity as determined by the investigator or reported to him/her by the patient. The assessment of severity is made irrespective of intervention relationship or seriousness of the event and should be evaluated according of the following scale:

- Mild: The event is noticeable to the patient, but is easily tolerated, and does not interfere with the patient's daily activities.
- Moderate: The event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- Severe: The event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

Note: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions.

Relationship to Treatment

For all events reported in patients exposed to Filsuvez, the treating physician or other reporting health care provider will be asked to assess the relationship of the AE/SAEs to Filsuvez using the following definitions:

- Probable: A causal relationship is clinically/biologically highly plausible, and there is a correlation between the onset of the AE/SAE and administration of the treatment, and between withdrawal of treatment and resolution of the AE/SAE.
- Possible: A causal relationship is clinically/biologically plausible and there is a correlation between the onset of the AE/SAE and administration of the treatment.

- Unlikely: A causal relationship is improbable, and another documented cause of the AE/SAE is most plausible.
- Unrelated: A causal relationship can be definitively excluded, and another documented cause of the AE/SAE is most plausible.

An adverse drug reaction is defined as a response to a medical product is noxious and unintended and which arise from the use of a medicinal product within the terms of marketing authorisation; the use outside the terms of marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors; and occupational exposure.

11.2 Procedures for Reporting AEs of Special Interest (AESIs) in the Case Report Form

All AESIs reported during the follow-up period will be captured on the appropriate study eCRF. Each AESI occurring during the study must be recorded in the appropriate eCRFs and/or specific AE forms as designated by Amryt, including the description, seriousness criteria, severity, duration (onset and resolution date), causal relationship with the study treatment, actions taken with the study treatment (dose reduction, withdrawal, etc.), any other required treatment, and outcome.

The outcome of each AE (serious or non-serious) should be entered with a term such as those described below:

- Recovered without sequelae
- Recovered with sequelae
- Ongoing
- Change in severity grade (worsening, improving)
- Died

If any of the same AEs occur on several occasions in the same patient, then the AE in question must be documented and assessed each time. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

11.3 Procedures for Reporting AEs to Amryt

All AESIs will be reported to Amryt via eCRF.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Interim Analyses and Reporting

Interim reports are planned every 2 years after study initiation and will be submitted to the EMA until the end of the study.

12.2 Final Analyses and Reporting

A final study report will be generated after all data collection is complete. The final study report will be submitted to the EMA within 12 months of the end of data collection. The final report will encompass all planned analyses, including a description of the complete study population.

In accordance with the 2010 EU pharmacovigilance legislation, information about this PASS will be entered into the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, interim reports where applicable, and the final study report will also be entered in the register.

12.3 Publications

Any publication of the results from this study must be consistent with Amryt's publication policy. The Study Steering Committee will assist in publication planning and manuscript review.

13 REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCePP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices.

Study title: A long-term non-interventional study to assess the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez (FOSteR)

EU PAS Register® number: To be added after registration
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	8

Comments:

This study is descriptive in nature, and no hypothesis testing is planned.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7

Section 3: Study design	**Yes**	**No**	**N/A**	**Section number**
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				9.2
4.2.1 Study time period	☒	☐	☐	
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1, 9.2.2

Comments:

Study has no age or sex restrictions.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1 9.7.2
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

The study drug, Filsuvez, does not have any direct comparator and is the first treatment approved for DEB and JEB indication.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.2.3,9.9
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.2.3,9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section number**
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g., International Classification of Diseases, Medical Dictionary for Regulatory Activities)	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.2
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2, 9.5, 9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: René Cordtz

Date: 20-Nov-2023

Signature: DocuSigned by Rene Cordtz
Rene Cordtz
I am the author of this document
20-Nov-2023 | 12:52:55 PM CET
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ANNEX 3. ADDITIONAL INFORMATION

The list of variables will be updated and adapted to local data source in SAP as required. Additional diagnosis codes, surgical and procedure codes, and laboratory tests may be added to the definition of individual variables, depending on the availability in the data sources; exact definitions will be included in the SAP.

Table 4: Inclusion and exclusion criteria

CRITERION	DEFINITION
Inclusion	
A confirmed diagnosis of DEB and JEB, and alive during the enrolment period	Records of diagnosis in the data source
Exclusion	
None	-

Abbreviations: DEB, Dystrophic epidermolysis bullosa; JEB, Junctional epidermolysis bullosa.

Table 5: Study outcomes

VARIABLE	DEFINITION
Primary outcome	
Skin malignancy (first occurrence)	First occurrence of any skin malignancy during the follow-up period in the DEB and JEB patients receiving treatment with Filsuvez recorded in the data source
Exploratory outcomes	
Skin malignancy (first occurrence)	First occurrence of any skin malignancy during the follow-up period in the DEB and JEB patients not receiving Filsuvez treatment
Skin malignancies by type (first occurrence of SCC, BCC, MM)	First occurrence of each type of skin malignancy during the follow-up in the DEB and JEB patients receiving Filsuvez treatment and not receiving Filsuvez treatment recorded in the data source
Skin malignancies (all occurrences combined)	All occurrences of skin malignancies including first and subsequent events, during the follow-up in the DEB and JEB patients exposed to and unexposed to Filsuvez, respectively, as recorded in the data source
Skin malignancies (all occurrences by type, de-novo and recurrent events)	De-novo and recurrent occurrences of skin malignancies, combined and separated into 2 distinct outcomes, including first and subsequent events, during follow-up in the DEB and JEB patients exposed to and unexposed to Filsuvez, respectively, as recorded in the data source
Patterns of Filsuvez use	
Filsuvez treatment at Filsuvez start date	e.g., application site and frequency at the treatment start date
Changes in Filsuvez treatment application frequency during follow-up	Treatment application frequency (based on dressing change frequency), treatment interruptions during follow-up
Filsuvez treatment discontinuation	e.g., proportion of patients who discontinue, time to discontinuation
Reasons for Filsuvez discontinuation during follow-up	Adverse reactions (like site reaction, pain, itching etc), treatment noncompliance, medication supply issues or other reasons
Characteristics of management of skin malignancy	-

VARIABLE	DEFINITION
Location, type and staging of skin malignancy (SCC, BCC and MM) (first and subsequent occurrences)	Record of location and type of skin malignancy (SCC, BCC and MM) in the data source Record of skin malignancy staging: TNM classification for SCC, BCC and AJCC classification for MM
Date of skin malignancy diagnosis (first and subsequent occurrences)	-
Type of diagnostic intervention (first and subsequent occurrences)	e.g., biopsy, imaging like CT scan, MRI etc.
Wound and/or skin characteristics, where malignancy was diagnosed	e.g., wound size, wound age, characteristics, such as hyperkeratosis, symptoms, such as pain
Treatment with Filsuvez	Yes/no, if yes, how long/frequent, frequency of dressing changes
Interventions on malignancy (first and subsequent occurrences)	Including medical treatment (chemotherapy, immunotherapy, radiotherapy, targeted therapies, and palliative care) and surgical excision
Malignancy outcome (first and subsequent occurrences)	e.g., recovered, remission, recurrence
Patient outcomes	e.g., mortality rate

Abbreviations: AJCC, American Joint Committee on Cancer; BCC, Basal cell carcinoma; CT, Computed tomography; DEB, Dystrophic epidermolysis bullosa; JEB, Junctional epidermolysis bullosa; MM, Malignant melanoma; MRI, Magnetic resonance imaging; SCC, Squamous cell carcinoma; TNM, Tumour, node and metastasis

Table 6: Censoring variables during follow-up

VARIABLE	DEFINITION
Death	Date of death
Discontinuation from registries or study sites	Death, discontinuation from site or registry, physician's decision in sites, withdrawal of consent, emigration, lost to follow-up, or end of the study
Filsuvez treatment for Filsuvez-unexposed patients	Start date of Filsuvez treatment
Discontinuation of Filsuvez use for Filsuvez-exposed (defined as Filsuvez non-use for more than 12 months)	Date of Filsuvez discontinuation for more than 12 months or date of initiation of alternative EB-specific treatment

Table 7: Other variables

VARIABLE	DEFINITION
Demographic characteristics	-
Age at index date	-
Sex	Biological sex
Race/ethnicity	-
Disease characteristics	-
EB diagnosis	Records of DEB or JEB diagnosis in the data source
Date of EB diagnosis	If unavailable, registry entry date
EB subtype	DDEB, RDEB and JEB overall
Wound characteristics	Wound size, location (trunk vs limbs)
Comorbidities at the index date	Records of diagnosis in the data source
Anaemia	-
Malnutrition	-
Previous diagnosis of skin malignancy at the index date	Diagnosis of skin malignancy prior to the index date recorded in the data source

Abbreviations: DDEB, Dominant dystrophic epidermolysis bullosa; DEB, Dystrophic epidermolysis bullosa; EB, Epidermolysis bullosa; JEB, Junctional epidermolysis bullosa; RDEB, Recessive dystrophic epidermolysis bullosa.