Non-Interventional Final Study Report

PASS Information

Title	BADBIR - British Association of Dermatologists Biologic Interventions Register
Version identifier of the final study report	1.0
Date of last version of the final study report	N/A
EU PAS register number	N/A
Active substance	Etanercept ATC code L04AB01
Medicinal product	Benepali
Product reference	H0004007
Procedure number	EMEA/VR/0000XXXXXX
Marketing authorisation	Samgsung Bioepis NL B.V.
Joint PASS	No
Research question and objectives	A nationwide registry which seeks to assess the long-term safety of biologic treatments for psoriasis. Recommended by National Institute for Health and Care Excellence (NICE) that all patients in the United Kingdom (UK) receiving new therapies for psoriasis be registered in
Country(-ies) of study	United Kingdom (UK) and Republic of Ireland (ROI)
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Table of Content

List of tables

1 Abstract

Title

BADBIR - British Association of Dermatologists Biologic Interventions Register

Keywords

Benepali, etanercept, psoriasis, long-term safety, BADBIR registry

Rationale and background

Psoriasis is a chronic inflammatory disease affecting 2-3% of the population. Biologic agents have emerged as effective treatments, but evidence primarily derives from short-term clinical trials of 3-6 months' duration. The British Association of Dermatologists Biologic Interventions Register (BADBIR) was established in 2007 to monitor the long-term safety of biologic treatments for psoriasis. As a Marketing Authorisation Holder (MAH) of Benepali, Samsung Bioepis NL B.V. committed to using BADBIR as a Post-Authorisation Safety Study (PASS) to evaluate the risk of selected adverse events in psoriasis patients treated with Benepali compared to conventional systemic therapies.

Research question and objectives

The objective of this study is to assess the risk of serious adverse events in psoriasis patients treated with Benepali compared to conventional systemic therapies with comparable disease severity.

Study design

This is a prospective observational cohort study with the primary aim to monitor the long-term safety of biologic interventions for psoriasis.

Setting

Patients were recruited from 85 dermatology centres across the United Kingdom and Republic of Ireland, with recruitment occurring from June 2016 to June 2021 and follow-up until July 2025.

Subjects and study size, including dropouts

The Benepali cohort comprised 451 patients, including 122 newly registered patients and 329 patients who switched from other biologic therapies, while the conventional cohort comprised 6,343 patients registered between September 2007 and the data cut-off date.

Variables and data sources

Baseline variables included age, gender, PASI, DLQI, smoking status, comorbidities, BMI, and previous UV therapy. Data were collected via online case report forms and linked to national healthcare databases such as NHS Digital for mortality, malignancy, and hospitalisation data.

Results

Total Serious Infection incidence was 26.3/1,000 person-years in the Benepali group versus 34.4/1,000 person-years in the conventional group (adjusted HR 0.74, 95% CI: 0.50-1.09). Skin (non-cancer) events were significantly lower in the Benepali group (adjusted HR 0.15, 95% CI: 0.04-0.60). Total Malignant Events

showed no statistically significant difference after adjustment (adjusted HR 1.17, 95% CI: 0.83-1.67). No tuberculosis, haematologic events, or lymphoproliferative disorders were reported in the Benepali cohort.

Discussion

Benepali was well-tolerated in psoriasis patients with no new safety signals identified. The safety profile is consistent with the established profile of etanercept. No new safety findings were observed that would change the current benefit-risk balance of Benepali, and the benefit-risk profile remains positive for use in the approved indication.

Marketing Authorisation Holder(s)

Samsung Bioepis NL B.VOlof Palmestraat 10
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Names and affiliations of principal investigators

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2 List of abbreviation

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
CAGE	Cut down, Annoyed, Guilty, Eye-opener (alcohol screening questionnaire)
cDLQI	Children's Dermatology Life Quality Index
CHF	Congestive Heart Failure
CI	Confidence Interval
cHAQ	Child Health Assessment Questionnaire
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimension
EQ-5D-y	EuroQol 5-Dimension Youth
ESI	Events of Special Interest
GPPASI	Generalised Pustular Psoriasis Area and Severity Index
GPPGA	Generalised Pustular Psoriasis Physician Global Assessment
HAQ	Health Assessment Questionnaire
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
IL	Interleukin
IR	Incidence Rate
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSSO	Maintenance and Support Services Organization
N/A	Not Applicable
NC	Not Calculated
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PASI	Psoriasis Area and Severity Index
PASS	Post-Authorisation Safety Study
PGA	Physician Global Assessment
PT	Preferred Term
PUVA	Psoralen plus Ultraviolet A
ROI	Republic of Ireland
RR	Relative Risk
SAE	Serious Adverse Event

Abbreviation	Definition
SAPASI	Self-Administered Psoriasis Area and Severity Index
SCC	Squamous Cell Carcinoma
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Rate
SOC	System Organ Class
TB	Tuberculosis
TNF	Tumor Necrosis Factor
UK	United Kingdom
UV	Ultraviolet
UVB	Ultraviolet B

3 Investigator

Name, Degree	Title	Affiliation
Richard Warren, BSc, MBChB, MRCP, PhD	Professor of Dermatology and Therapeutics	The University of Manchester, Manchester, UK.
BADBIR Study Group	N/A	The University of Manchester, Manchester, UK.

4 parties

Not applicable

5 Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	May 2016	May 2016	N/A
End of data collection	Jul 31, 2025	Jul 31, 2025	N/A
Registration in the EU PAS register	N/A	N/A	Since the PASS is categorized as Category 3, it was not registered in the EU PAS register

6 Rationale and background

Psoriasis is a chronic, lifelong inflammatory disease affecting approximately 2-3% of the population, with onset typically before age 40. Biologic interventions using highly specific immuno-modulatory agents have emerged as effective treatments for moderate to severe psoriasis, particularly when conventional systemic therapies have failed or are contraindicated. Currently, the therapeutic landscape for psoriasis is expanding with increasing availability of biologic agents, including TNF inhibitors, IL-17A inhibitors, IL-12 inhibitors, and IL-12/23 inhibitors, as well as their biosimilars. However, the evidence base for these therapies derives primarily from short-term randomised clinical trials of 3-6 months' duration, whilst psoriasis requires lifelong management.

Meanwhile, increased mortality and various comorbidities have been observed in patients with psoriasis. Patients with severe psoriasis have significantly increased mortality, particularly from cardiovascular disease [3, 5, 7], and face cumulative exposure to potentially toxic therapies over decades. Observational studies have demonstrated that severe psoriasis itself is associated with increased cancer risks, including lymphoma with a relative rate of 2.95 [2] and a risk ratio of 7.95 in patients requiring second-line therapy [6]. Boffetta, Gridley, and Lindelof [1] reported increased overall cancer risk (Standardized Incidence Ratio; SIR 1.37) with notable increases in squamous carcinoma of the skin (SIR 2.64). Similarly, Hannuksela-Svahn et al. [4] found increased incidence of Hodgkin's disease (RR 3.3), non-Hodgkin's lymphoma (SIR 2.2), and squamous carcinoma of the skin (SIR 3.2) in hospitalised psoriasis patients. However, it remains unclear whether these risks are attributable to disease severity or cumulative treatment effects.

Biologics offer considerable benefits but questions persist regarding long-term safety, safety in pregnancy and childhood, optimal treatment sequencing, relative drug survival, and the use of co-therapies, and those questions cannot be answered by short-term clinical trials alone. The British Association of Dermatologists Biologic Interventions Register (BADBIR) began in September 2007 under the auspices of the British Association of Dermatologists (BAD) and is based at the University of Manchester, UK. On Jan 14, 2016, EMA accepted the proposal of Marketing Authorisation Holder (MAH) to commit BADBIR, as a Post-Authorisation Safety Study (PASS) to provide long term safety data on the use of Benepali in patients with psoriasis. Therefore, this study is designed to evaluate the risk of selected adverse events in psoriasis patients treated with biologic agents compared to conventional systemic therapies.

7 Research question and objectives

The objective of this study is to assess the risk of serious adverse events in psoriasis patients treated with biologic agents compared to conventional systemic therapies with comparable disease severity. This assessment includes potential adverse effects which may not have been detected in short-term clinical trials, specifically cancer (particularly lymphoma), non-melanoma skin cancer (especially squamous cell carcinoma), demyelinating disease, and tuberculosis.

8 Amendments and updates to the protocol

Version	Date	Section of study protocol	Amendment or update	Reason
17	Aug 01, 2017	Section #2	Separated participant with 16 years of age and under 16 years of age. Therefore separating: Patient information sheet, Patient consent form, Particiapnt consent form (parent/guardian)	N/A
18	Jun 01, 2018	Section #6 Section #7	HADS (The hospital anxiety and depression scale) added to follow-up data collection HADS added to baseline questionnaires	N/A
19	Jun 01, 2020	Section #1 Section #3 Section #4 Section #8 Section #9	Steering Group changes Licensed Biologics count: Six originator biologics (3 TNF, 2 IL-17A, 1 IL12/23) changed to Eleven originator biologics (4 TNF including Cimzia, 3 IL-17A including Kyntheum, 3 IL-12 including Ilumetri/Skyrizi/Tremfya, 1 IL12/23) Recruitment discontinuation of Humira Follow-up questionnaire added: Appointment section with "Did the most recent follow-up take place in-person or remotely (e.g. phone, video)?" and "Date of most recent appointment" Prior therapy biosimilar list included: Amgevita, Hyrimoz, Ilumetri, Imraldi, Kyntheum, Skyrizi, Tremfya, Zessly	N/A
20	Aug 01, 2022	Section #1 Section #3 Section #6 Section #7 Section #8 Section #9	Steering Group changes Study end definition: Study end is defined as when the last participants have completed their final visits. Baseline severity added: Generalised Pustular Psoriasis diagnosis: Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) and date taken Arthritis follow-up: HAQ/CHAQ "every 6 months up to Follow up 6 (month 36) – Newly added: and annually thereafter (month 48, 60 etc.) Prior therapy list to include: Bimzelx (bimekizumab), Idacio (adalimumab biosimilar), New Small Molecule Immunomodulatory Therapies" with Otezla (apremilast), Skilarence (dimethyl fumarate) Follow-up data collection period: at follow up six monthly to Month 36 (Year 3) - Newly added: and annually thereafter (year 4+)	N/A
21	Sep 21, 2024	Section #1 Section #3 Section #4 Section #5 Section #6	Steering Group changes Licensed Biologics count: Eleven → Twelve originator biosimilars, Bimzelx moved to IL-17A inhibitors category (now 4 IL-17A inhibitors) New small molecule therapies: Deucravacitinib (Sotyktu) to the small molecule immunotherapies list New Biologics Therapy List: Hulio (adalimumab biosimilar), Yuflyma (adalimumab), Spevigo (spesolimab) added Study End Date Defined: Patient recruitment ends:	N/A

Version	Date	Section of study protocol	Amendment or update	Reason
			31/07/2027 All patients followed-up until: 31/07/2028After 31/07/2028: No new data input from sites	
		Section #7	Paediatric Patients Section: New dedicated section for paediatric patients with specific inclusion criteria: 1. Patient starting/commencing systemic therapy in last 6 months 2. Any systemic treatment allowed (not limited to eligible drugs list) 3. cDLQI of 10+ NOT required for patients under 16 4. Consent requirements: Under 11 = parent/guardian consent; Ages 11-16 = Assent + Parent/guardian consent 5. Re-consent required at age 16	
		Section #8	Comparator Cohort Inclusion Criteria Changes: Significantly revised inclusion criteria: 1. PASI ≥10 AND DLQI >10 required for moderate to severe psoriasis 2.Switching between conventional therapies: historic PASI ≥10 and DLQI >10 required 3. GPP patients: Can initiate/switch to methotrexate, ciclosporin, acitretin WITHOUT meeting PASI/DLQI criteria	
		Section #9	Consent Process Updates (V21 Section 5): Detailed postal consent procedures added: Patient must sign consent within 6 months of starting registration drug Multiple return options (post, photo/scan email) Local approval required for email exchange	
		Section #11	Data Collection Method Updates: (V21 Section 7) Enhanced quality control measures: 1. All staff must complete online training prior to database access 2. Database Query System added 3.Centre audits to verify source data	
		Section #13	GPP Flare Data Collection (V21 Section 9.2): New GPP-specific data fields: 1. Recent hospitalization for GPP flare (Yes/No) 2. Date of admission 3. GPPGA on admission 4. Time to pustular clearance GPPGA/GPPASI at Week 1, 2, and 3 4. Possible trigger for flare	

9 Research methods

9.1 Study design

The BADBIR is a prospective observational cohort study, with the primary aim to monitor the long-term safety of new biologic interventions for psoriasis. Data are collected from patients and clinicians/nurses on a regular basis to assess changes in therapy and to obtain information regarding adverse events. Patient records are also linked to national cancer and death registers to provide lifelong follow-up.

9.2 Settings

The data used in the current report was extracted from BADBIR, in which information is prospectively collected. Patients were recruited from 85 dermatology centres across the UK and Republic of Ireland with good geographic spread. Recruitment for the Benepali cohort occurred between Jun 16, 2016 and Jul 31, 2021, with follow-up until Jul 31, 2025.

At baseline, the dermatology clinician and/or nurse completes registration form including diagnosis, disease activity (PASI), previous and current anti-psoriatic therapies, comorbidities, and medication lists using the online database available via the BADBIR website (http://www.badbir.org/). Standardised patient-reported outcome measures including DLQI, EuroQol, CAGE, and HAQ (for patients with inflammatory arthritis) are also collected. Data for both Benepali and conventional cohorts are collected identically.

Follow-up data are collected six-monthly for the first three years and yearly thereafter until study end. To ensure comprehensive data, BADBIR links with national healthcare data providers (e.g., NHS Digital in England) to receive information on mortality, malignancy, and inpatient hospital admissions. Patient data are pseudonymised to protect confidentiality.

9.3 Subjects

The following patients were eligible to participate in the Benepali cohort of the BADBIR:

i. Willingness to give informed consent to participate in the study
ii. Diagnosis of psoriasis under the care of a dermatologist
iii. Started on, or switched to, Benepali within previous 6 months
iv. Biologic-naïve

The following patients were eligible to participate in the comparison cohort of the BADBIR:

i. Willingness to give informed consent to participate in the study
ii. Diagnosis of psoriasis under the care of a dermatologist
iii. Started on, or switched to, a conventional systemic therapy (acitretin, ciclosporin, fumaric acid esters, hydroxycarbamide, methotrexate, PUVA) within previous 6 months
iv. PASI≥10 and DLQI>10 (unless switching between conventional systemics)
v. Biologic-naïve

9.4 Variables

9.4.1 Treatment exposure

Treatment exposure is categorized into the following two cohorts:

- Benepali cohort: Patients started on or switched to Benepali

- Comparison cohort: Patients started on, or switched to, a conventional systemic therapy (acitretin, ciclosporin, fumaric acid esters, hydroxycarbamide, methotrexate, PUVA)

9.4.2 Outcomes

The following pre-selected events, which were agreed at a European Meeting (Manchester 2002) involving three rheumatology Biologics Registers (UK, Sweden and Germany) alongside the pharmaceutical companies that market biologic therapy and form the basis for the "Manchester Template", and death were analyzed:

- Aplastic anaemia, pancytopaenia, serious neutropenia
- Cerebrovascular accident (CVA)
- Hepatitis B reactivation
- Lymphoproliferative disease
- Malignancy (not including skin)
- Melanoma or skin cancer including Bowen's disease
- Myocardial infarction / acute coronary disease
- Pregnancy
- Pulmonary embolism
- Serious demyelination / optic neuritis
- Serious congestive heart failure
- Serious hepatic dysfunction/failure
- Serious hypersensitivity reaction
- Serious infection (excluding tuberculosis)
- Serious lupus / lupus-like illness
- Serious psoriasis flare
- Serious skin reaction (e.g. Stevens Johnson syndrome, erythema multiforme toxic epidermal necrolysis)
- Surgery (overnight hospitalisation)
- Tuberculosis (not latent)

9.4.3 Baseline covariates

i. Patient identification and demographics
- Date of Birth
- Gender
- Patient identification unique number
- Date of consent

ii. Psoriasis details
- Type of psoriasis
- Year of onset of psoriasis
- Family history of psoriasis in first degree relatives (Yes or No)
- Psoriatic arthritis (Yes or No)

iii. Baseline severity
- Psoriasis Area and Severity Index (PASI) and date taken
- Physician Global Assessment (PGA) and date taken
- Generalised Pustular Psoriasis diagnosis: Generalised Pustular Psoriasis Area and Severity Index (GPPASI) and date taken
- Generalised Pustular Psoriasis diagnosis: Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) and date taken

iv. Current Treatment

- Registration Treatment name, starting date, dose and frequency (For all cohorts)
- Name and start date of any other systemic treatment

v. Prior therapy

- Has the patient previously received and total exposure (months): conventional systemics, biologics, new small molecule immunomodulatory therapies

vi. UV therapy history

vii. Comorbidities

viii. Skin

- Fitzpatrick Skin Type (Fitzpatrick,1975)
- Outdoor occupation
- Residence in tropical/subtropical countries
- History of prior Neoplastic or pre-cancerous lesions
- Melanoma, Melanoma in situ (give site and date for each), SCC (give number), BCC (give number), yes tick for Keratoacanthoma, Actinic Keratosis, Bowen's Disease.

i. Laboratory investigations

ii. Additional Measurements

iii. Patient Completed Questionnaires

- Patient Baseline Questionnaire (including birth place, ethnicity, working status, alcohol intake, current and historic smoking).
- DLQI or cDLQI
- EuroQol or EQ-5D-y
- CAGE
- HAQ (if patient is diagnosed with inflammatory arthritis) or cHAQ
- HADS
- Self-Administered PASI
- PGA (patient completed)

9.5 Data sources and measurement

Data are collected via an online Case Report Form, completed by clinical nurse specialists or research nurses at dermatology units. Follow-up data were collected every six months for the first three years and annually thereafter until study end. All patients were flagged with national healthcare data providers (e.g., NHS Digital in England) to capture additional information on mortality, malignancy, and overnight hospital admissions. All BADBIR data, including those from national healthcare providers, were entered into an online database accessible via the BADBIR website (http://www.badbir.org/). When formal follow-up of the last patients entered in the register was complete, BADBIR continued to link the register to the national providers of healthcare data.

9.6 Bias

To minimize selection bias, control groups who must never have been exposed to biologic therapy, will be recruited across all contributing centres with a target of one control per patient. The primary purpose of the study is to ascertain whether there is an increased risk of events in the Benepali cohort compared to the conventional cohort with comparable disease severity. To reduce bias between groups, BADBIR collected at baseline the reasons for treatment with the chosen agent, including intolerance, contraindication, or failure to respond to other therapies. To address potential bias from treatment switching, person-years of follow-up will be reassigned from the comparator group to the exposed group upon initiation of biologic therapy.

9.7 Study size

The number of patient-years exposure required in each cohort to detect different risk ratios between biologics and conventional interventions were calculated for a two-sided significance of $\alpha < 0.05$ to be detected with 80% power. BADBIR aimed to recruit 4000 patients on conventional therapies and 2000-4000 on Benepali intervention.

9.8 Data transformation and groups

Data for both the Benepali and conventional cohorts were collected in an identical manner through the BADBIR online database. For the baseline characteristics, age and disease duration are presented in years, PASI and DLQI are presented as scores, previous UV therapy is categorised as yes or no, smoking status is categorised as never, previous, or current, number of comorbidities is categorised as 0, 1-2, 3-4, or 5+, and body mass index is categorised as <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, or 40+ kg/m².

All adverse events were categorised as either serious or non-serious and entered into the online database by clinical or research team members at each participating centre. Events identified through national database linkage were electronically received and entered by the pharmacovigilance team. Event rates were expressed as incidence rates per 1,000 person-years with 95% confidence intervals. Patients were grouped into two main cohorts: the Benepali cohort and the conventional cohort.

9.9 Statistical methods

9.9.1 Main summary measures

Baseline characteristics were summarised using means and standard deviations for continuous variables (age, disease duration, PASI, DLQI, body mass index) and frequencies and percentages for categorical variables (gender, smoking status, number of comorbidities, previous UV therapy).

The number of events stratified by sex per treatment group was presented in the table. Event rates were expressed as incidence rates per 1,000 person-years with 95% confidence intervals. Both unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals were calculated using Cox proportional hazards models.

9.9.2 Main statistical methods

Incidence Rate Calculation

Incidence rates per 1,000 person-years were calculated with two approaches as below:

- All events: Including all occurrences of each serious adverse event within the qualifying exposure window, allowing for recurrent events
- First events only: Censoring patients at their first event, counting only one event per individual

Comparison Between Groups

Comparisons between Benepali and conventional groups were performed using Cox proportional hazards models. Only time to first outcome was analysed. A comparison was made only when at least one event had been observed in each group. Both unadjusted and adjusted hazard ratios were reported.

Control for Confounding

The models were adjusted using deciles of a propensity score calculated using the following baseline variables:

- Age

- Sex
- Disease duration
- PASI
- DLQI
- Previous UV therapy
- Smoking status
- Number of comorbidities
- Body mass index
- Interaction terms: Age×Sex, Age×Disease Duration, Age×Number of Comorbidities

Calculation of Exposure and Risk Windows

Incidence rates were calculated based on outcome-specific risk windows:

- For all adverse events except malignancy and death: The risk window began at the start of the index biologic agent and continued until 90 days after therapy discontinuation, death, or end of data collection, whichever occurred first. If a patient started a second biologic agent within 90 days of discontinuing the first, risk windows overlapped and both agents were credited for any serious adverse event.
- For malignancy: The risk window included all person-time from the start of biologic therapy and extended until the cut-off date (31st July 2025) or death, even if the patient switched to another biologic agent.
- For death: The risk window began at the start of therapy and continued until 90 days after therapy discontinuation, death, or the cut-off date.

9.9.3 Missing values

Missing baseline data were replaced using multiple imputation, with 20 datasets generated.

9.9.4 Sensitivity analyses

No sensitivity analyses were conducted in this study.

9.9.5 Amendments to the statistical analysis plan

No amendment has been made to this statistical analysis plan.

9.10 Quality control

The following coordinated program ensured quality control

i. Training of staff – including a program of training for nurses in PASI scoring and how to use the register. A coordinated program was underway.
ii. An on-line manual was provided for dermatologists to send in quality data, including worksheets for collection of data.
iii. Quality checks were made for data received (i.e. manual scanning for completeness, errors and then checks at data entry stage for inconsistencies).
iv. Selected serious adverse events (SAEs) were checked against a set of predefined validation criteria.

10 Results

10.1 Participants

As of Jul 31, 2025, a total of 451 patients were registered in the Benepali cohort, comprising 122 newly registered patients and 329 patients who switched to Benepali from another biologic therapy. Patients were recruited into the Benepali cohort from 85 centres across the UK and the ROI. The conventional cohort comprised 6,343 patients registered between Sep 27, 2007 and the data cut-off date.

10.2 Descriptive data

The baseline characteristics of the two cohorts are presented in Table 1, Table 2, and Table 3.

The Benepali cohort included 188 females and 263 males, with males being slightly more prevalent. Male patients in the Benepali cohort had a mean age of 47.2 (12.4) years compared with 43.9 (14.0) years in the conventional cohort. Female patients in the Benepali cohort had a mean age of 46.6 (14.2) years compared with 42.9 (15.1) years in the conventional cohort. Patients in the Benepali cohort had a longer mean disease duration compared with the conventional cohort (23.9 vs 18.0 years). Patients in the conventional cohort had slightly higher PASI (15.2 vs 13.6) and DLQI (15.8 vs 13.8) scores at baseline compared with the Benepali cohort.

A higher proportion of patients in the Benepali cohort had received previous UV therapy compared with the conventional cohort. The conventional cohort had a higher proportion of current smokers compared with the Benepali cohort (32.6% vs 24.6%). In both cohorts, patients with 1-2 comorbidities comprised the largest proportion. A higher proportion of patients in the Benepali cohort had 1-2 comorbidities compared with the conventional cohort (69.6% vs 55.0%), while a higher proportion of patients in the conventional cohort had no comorbidities (36.1% vs 21.7%). A higher proportion of patients in the Benepali cohort were in the obese categories (BMI ≥30) compared with the conventional cohort (47.5% vs 43.6%).

Table 1. Baseline demographic characteristics of patients registered in the conventional and Benepali cohorts

		Benepali	Conventional
Cumulative number of registrations		122	6,343
Cumulative number by gender	Male	73	3,565
	Female	49	2,778
Cumulative number by age at registration	Under 16	0	58
	16-18	3	109
	19-34	31	1,826
	35-44	19	1,499
	45-54	39	1,441
	55-64	21	886
	65-74	8	420
	75 +	1	104
Cumulative number of switchers		329	
Cumulative number by gender	Male	190	
	Female	139	
Cumulative number by age at registration	Under 16	0	
	16-18	1	
	19-34	51	
	35-44	83	
	45-54	104	
	55-64	59	
	65-74	27	
	75 +	4	
Cumulative number of patients registered in cohort		451	6,343

Table 2. Baseline disease characteristics of patients registered in the conventional and Benepali cohorts

		Benepali			Conventional		
		N	**Mean**	**SD**	**N**	**Mean**	**SD**
Age (years)	Male	263	47.2	12.4	3,565	43.9	14.0
	Female	188	46.6	14.2	2,778	42.9	15.1
	Total	451	46.9	13.1	6,343	43.5	14.5
Disease Duration (years)	Male	263	23.1	12.3	3,553	17.0	12.3
	Female	188	25.1	13.6	2,772	19.2	14.2
	Total	451	23.9	12.9	6,325	18.0	13.2
PASI	Male	263	13.8	7.1	3,564	15.6	8.2
	Female	188	13.4	7.7	2,776	14.7	7.5
	Total	451	13.6	7.3	6,340	15.2	7.9
DLQI	Male	258	13.4	8.7	3,537	15.3	6.8
	Female	186	14.2	8.6	2,756	16.4	6.8
	Total	444	13.8	8.6	6,293	15.8	6.8

Table 3. Baseline previous UV therapy, smoking status, number of comorbidities and body mass index of patients registered in the conventional and Benepali cohorts

		Benepali N (%)	Conventional N (%)
Previous UV Therapy	Yes	337 (74.7%)	4,355 (68.7%)
	No	114 (25.3%)	1,988 (31.3%)
	Total	451	6,343
Smoking status	Never	144 (37.7%)	1,855 (32.9%)
	Previous	144 (37.7%)	1,940 (34.4%)
	Current	94 (24.6%)	1,838 (32.6%)
	Total	382	5,633
Number of comorbidities	0	98 (21.7%)	2,289 (36.1%)
	1-2	314 (69.6%)	3,491 (55.0%)
	3-4	32 (7.1%)	435 (6.9%)
	5+	7 (1.6%)	128 (2.0%)
	Total	451	6,343
Body mass index	<18.5	5 (1.2%)	97 (1.7%)
	18.5-24.9	67 (16.3%)	1,297 (22.3%)
	25-29.9	144 (35.0%)	1,885 (32.4%)
	30-34.9	99 (24.0%)	1,379 (23.7%)
	35-39.9	66 (16.0%)	622 (10.7%)
	40+	31 (7.5%)	533 (9.2%)
	Total	412	5,813

10.3 Outcome data

A detailed description of the number of patients to evaluate targets is provided within Section 10.12.

10.4 Main results

This analysis included 6,343 in the conventional group, and 451 in the Benepali group. Table 4 shows the number of events and crude rates of all events listed by treatment group. All groups have the highest incidence rate in "Total Serious Infection" among SAE listed in the Table 4. In the crude rates analysis, Total Serious Infection was less frequently reported in the Benepali group compared to the conventional group [26.3 (95% CI: 18.9-35.6) vs. 34.4 (95% CI: 32.2-36.7)], while Respiratory (non-infection) events showed a slightly higher rate in the Benepali group [7.0 (95% CI: 3.5-12.6) vs. 5.0 (95% CI: 4.2-5.9)]. Cardiac SAEs showed a slightly higher incidence rate in the Benepali group compared to the conventional group [12.2 (95% CI: 7.3-19.0) vs. 11.5 (95% CI: 10.3-12.8)]. When stratified by sex, this pattern was consistent among females [11.1 (95% CI: 4.5-22.9) vs. 7.1 (95% CI: 5.7-8.8)], whereas males showed a higher incidence rate in the conventional group compared to the Benepali group [12.9 (95% CI: 6.7-22.5) vs. 15.1 (95% CI: 13.2-17.2)]. Nervous System SAEs and Skin (non-cancer) events were less frequent in the Benepali group [5.1 (95% CI: 2.2-10.1) vs. 7.2 (95% CI: 6.3-8.3) and 3.2 (95% CI: 1.0-7.5) vs. 10.7 (95% CI: 9.5-12.0), respectively]. No TB or haematologic events were reported in the Benepali group during the study. For Total Malignant Events, the Benepali group showed a higher incidence rate compared to the conventional group [18.2 (95% CI: 13.9-23.3) vs. 7.6 (95% CI: 6.9-8.3)], primarily driven by elevated rates of Skin Cancer [10.4 (95% CI: 7.3-14.5) vs. 3.1 (95% CI: 2.7-3.6)] and Solid Tumours [7.4 (95% CI: 4.8-11.0) vs. 4.1 (95% CI: 3.6-4.6)]. Death rates showed a slightly higher incidence rate in the Benepali group compared to the conventional group [5.6 (95% CI: 2.6-10.7) vs. 4.2 (95% CI: 3.7-4.7)]. In sex-specific analyses, this pattern was consistent among females [9.2 (95% CI: 3.4-20.1) vs. 3.5 (95% CI: 2.8-4.2)], whereas males showed a higher incidence rate in the conventional group compared to the Benepali group [3.2 (95% CI: 0.7-9.2) vs. 4.7 (95% CI: 4.1-5.5)]. Apart from cardiac SAEs and death, no other events showed sex-specific incidence rate patterns that differed from the total population results.

The number and rates of first events, including unadjusted and adjusted hazard ratios, are presented in Table 5. Regarding the incidence rate, when censoring patients at their first event as shown in Table 5, death showed a higher rate in the conventional therapy group compared with the Benepali therapy group (4.17 vs. 2.71), which is opposite to the result calculated using the full qualifying exposure window (4.2 vs. 5.6). Except for death, the incidence rates of SAEs showed consistent results between the two methods.

Among all SAEs, only Skin (non cancer) showed a statistically significant difference, with an adjusted HR of 0.15 (95% CI: 0.04-0.60). For other SAEs, no statistically significant differences were observed. Respiratory (non-infection) (HR 1.60, 95% CI: 0.82-3.11), Total Malignant Events (HR 1.17, 95% CI: 0.83-1.67), Skin Cancer (HR 1.28, 95% CI: 0.75-2.18), Other Cardiac Events (adjusted HR 1.24, 95% CI: 0.66-2.31) showed numerically higher risk with Benepali, while Total Serious Infection (HR 0.74, 95% CI: 0.50-1.09), Death (HR 0.56, 95% CI: 0.28-1.09), Nervous System SAE (HR 0.67, 95% CI: 0.31-1.44), and Cardiac SAE(HR 0.99, 95% CI: 0.58-1.68) showed numerically lower risk with Benepali.

Table 4. Results of safety analysis: Crude rates of all events listed in the Manchester Template

Event	Conventional (n=6,343)						Benepali (n=451)					
	Males		Females		Total		Males		Females		Total	
	Events	IR/1,000PY (95% CI)	Events	IR/1,000 PY (95% CI)	Events	IR/1,000PY (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)
Total Serious Infection	**500**	**33.3 (30.4, 36.3)**	**442**	**35.8 (32.5, 39.3)**	**942**	**34.4 (32.2, 36.7)**	**23**	**24.7 (15.7, 37.1)**	**18**	**28.5 (16.9, 45.1)**	**41**	**26.3 (18.9, 35.6)**
Pneumonia	165	11.0 (9.4, 12.8)	108	8.7 (7.2, 10.6)	273	10.0 (8.8, 11.2)	8	8.6 (3.7, 17.0)	3	4.8 (1.0, 13.9)	11	7.0 (3.5, 12.6)
Septicaemia	56	3.7 (2.8, 4.8)	46	3.7 (2.7, 5.0)	102	3.7 (3.0, 4.5)	1	1.1 (0.0, 6.0)	0	0.0 (0.0, 5.8)	1	0.6 (0.0, 3.6)
Bone/Joint infection	23	1.5 (1.0, 2.3)	3	0.2 (0.1, 0.7)	26	0.9 (0.6, 1.4)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Opportunistic infection	4	0.3 (0.1, 0.7)	3	0.2 (0.1, 0.7)	7	0.3 (0.1, 0.5)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Soft tissue and skin infection	74	4.9 (3.9, 6.2)	81	6.6 (5.2, 8.1)	155	5.7 (4.8, 6.6)	7	7.5 (3.0, 15.5)	3	4.8 (1.0, 13.9)	10	6.4 (3.1, 11.8)
Cellulitis	40	2.7 (1.9, 3.6)	43	3.5 (2.5, 4.7)	83	3.0 (2.4, 3.8)	2	2.2 (0.3, 7.8)	1	1.6 (0.0, 8.8)	3	1.9 (0.4, 5.6)
Other soft tissue and skin infection	34	2.3 (1.6, 3.2)	38	3.1 (2.2, 4.2)	72	2.6 (2.1, 3.3)	5	5.4 (1.7, 12.6)	2	3.2 (0.4, 11.5)	7	4.5 (1.8, 9.2)
Other serious infection	178	11.8 (10.2, 13.7)	201	16.3 (14.1, 18.7)	379	13.8 (12.5, 15.3)	7	7.5 (3.0, 15.5)	12	19.0 (9.8, 33.2)	19	12.2 (7.3, 19.0)
TB	**1**	**0.1 (0.0, 0.4)**	**0**	**0.0 (0.0, 0.3)**	**1**	**0.0 (0.0, 0.2)**	**0**	**0.0 (0.0, 4.0)**	**0**	**0.0 (0.0, 5.8)**	**0**	**0.0 (0.0, 2.4)**
Respiratory (non-infection)	**79**	**5.3 (4.2, 6.6)**	**57**	**4.6 (3.5, 6.0)**	**136**	**5.0 (4.2, 5.9)**	**7**	**7.5 (3.0, 15.5)**	**4**	**6.3 (1.7, 16.2)**	**11**	**7.0 (3.5, 12.6)**
Cardiac SAE	**227**	**15.1 (13.2, 17.2)**	**88**	**7.1 (5.7, 8.8)**	**315**	**11.5 (10.3, 12.8)**	**12**	**12.9 (6.7, 22.5)**	**7**	**11.1 (4.5, 22.9)**	**19**	**12.2 (7.3, 19.0)**
CHF (new or worsening)	45	3.0 (2.2, 4.0)	13	1.1 (0.6, 1.8)	58	2.1 (1.6, 2.7)	3	3.2 (0.7, 9.4)	2	3.2 (0.4, 11.5)	5	3.2 (1.0, 7.5)

Event	Conventional (n=6,343)						Benepali (n=451)					
	Males		Females		Total		Males		Females		Total	
	Events	IR/1,000PY (95% CI)	Events	IR/1,000 PY (95% CI)	Events	IR/1,000PY (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)
Myocardial infarction	73	4.9 (3.8, 6.1)	19	1.5 (0.9, 2.4)	92	3.4 (2.7, 4.1)	2	2.2 (0.3, 7.8)	1	1.6 (0.0, 8.8)	3	1.9 (0.4, 5.6)
Other cardiac events	109	7.3 (6.0, 8.8)	56	4.5 (3.4, 5.9)	165	6.0 (5.1, 7.0)	7	7.5 (3.0, 15.5)	4	6.3 (1.7, 16.2)	11	7.0 (3.5, 12.6)
Nervous System SAE	**121**	**8.1 (6.7, 9.6)**	**77**	**6.2 (4.9, 7.8)**	**198**	**7.2 (6.3, 8.3)**	**3**	**3.2 (0.7, 9.4)**	**5**	**7.9 (2.6, 18.5)**	**8**	**5.1 (2.2, 10.1)**
Central Demyelination	0	0.0 (0.0, 0.2)	0	0.0 (0.0, 0.3)	0	0.0 (0.0, 0.1)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Peripheral neuropathy	2	0.1 (0.0, 0.5)	2	0.2 (0.0, 0.6)	4	0.1 (0.0, 0.4)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Seizures	11	0.7 (0.4, 1.3)	13	1.1 (0.6, 1.8)	24	0.9 (0.6, 1.3)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Cerebrovascular Accident	67	4.5 (3.5, 5.7)	27	2.2 (1.4, 3.2)	94	3.4 (2.8, 4.2)	1	1.1 (0.0, 6.0)	1	1.6 (0.0, 8.8)	2	1.3 (0.2, 4.6)
Other CNS	41	2.7 (2.0, 3.7)	35	2.8 (2.0, 3.9)	76	2.8 (2.2, 3.5)	2	2.2 (0.3, 7.8)	4	6.3 (1.7, 16.2)	6	3.8 (1.4, 8.4)
Skin (non cancer)	**163**	**10.8 (9.2, 12.6)**	**130**	**10.5 (8.8, 12.5)**	**293**	**10.7 (9.5, 12.0)**	**5**	**5.4 (1.7, 12.6)**	**0**	**0.0 (0.0, 5.8)**	**5**	**3.2 (1.0, 7.5)**
Total haematologic events	**11**	**0.7 (0.4, 1.3)**	**9**	**0.7 (0.3, 1.4)**	**20**	**0.7 (0.4, 1.1)**	**0**	**0.0 (0.0, 4.0)**	**0**	**0.0 (0.0, 5.8)**	**0**	**0.0 (0.0, 2.4)**
Aplastic anaemia	2	0.1 (0.0, 0.5)	1	0.1 (0.0, 0.5)	3	0.1 (0.0, 0.3)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Pancytopaenia	2	0.1 (0.0, 0.5)	0	0.0 (0.0, 0.3)	2	0.1 (0.0, 0.3)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Agranulocytosis	0	0.0 (0.0, 0.2)	1	0.1 (0.0, 0.5)	1	0.0 (0.0, 0.2)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)
Other dyscrasia	7	0.5 (0.2, 1.0)	7	0.6 (0.2, 1.2)	14	0.5 (0.3, 0.9)	0	0.0 (0.0, 4.0)	0	0.0 (0.0, 5.8)	0	0.0 (0.0, 2.4)

Event	Conventional (n=6,343)						Benepali (n=451)					
	Males		Females		Total		Males		Females		Total	
	Events	IR/1,000PY (95% CI)	Events	IR/1,000 PY (95% CI)	Events	IR/1,000PY (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)
Total malignant events	**303**	**8.0 (7.2, 9.0)**	**203**	**7.0 (6.1, 8.0)**	**506**	**7.6 (6.9, 8.3)**	**30**	**15.3 (10.3, 21.9)**	**31**	**22.1 (15.0, 31.4)**	**61**	**18.2 (13.9, 23.3)**
Lymphoproliferative	12	0.3 (0.2, 0.6)	12	0.4 (0.2, 0.7)	24	0.4 (0.2, 0.5)	0	0.0 (0.0, 1.9)	0	0.0 (0.0, 2.6)	0	0.0 (0.0, 1.1)
Lymphoma	9	0.2 (0.1, 0.5)	8	0.3 (0.1, 0.5)	17	0.3 (0.1, 0.4)	0	0.0 (0.0, 1.9)	0	0.0 (0.0, 2.6)	0	0.0 (0.0, 1.1)
Myeloma	0	0.0 (0.0, 0.1)	3	0.1 (0.0, 0.3)	3	0.0 (0.0, 0.1)	0	0.0 (0.0, 1.9)	0	0.0 (0.0, 2.6)	0	0.0 (0.0, 1.1)
Leukaemia	3	0.1 (0.0, 0.2)	1	0.0 (0.0, 0.2)	4	0.1 (0.0, 0.2)	0	0.0 (0.0, 1.9)	0	0.0 (0.0, 2.6)	0	0.0 (0.0, 1.1)
Skin Cancer	143	3.8 (3.2, 4.5)	65	2.2 (1.7, 2.9)	208	3.1 (2.7, 3.6)	16	8.2 (4.7, 13.3)	19	13.6 (8.2, 21.2)	35	10.4 (7.3, 14.5)
Non Melanoma Skin Cancer	134	3.6 (3.0, 4.2)	56	1.9 (1.5, 2.5)	190	2.9 (2.5, 3.3)	15	7.7 (4.3, 12.6)	18	12.9 (7.6, 20.3)	33	9.8 (6.8, 13.8)
Melanoma	7	0.2 (0.1, 0.4)	9	0.3 (0.1, 0.6)	16	0.2 (0.1, 0.4)	0	0.0 (0.0, 1.9)	1	0.7 (0.0, 4.0)	1	0.3 (0.0, 1.7)
Other Skin Cancer	2	0.1 (0.0, 0.2)	0	0.0 (0.0, 0.1)	2	0.0 (0.0, 0.1)	1	0.5 (0.0, 2.8)	0	0.0 (0.0, 2.6)	1	0.3 (0.0, 1.7)
Solid tumours	147	3.9 (3.3, 4.6)	124	4.3 (3.6, 5.1)	271	4.1 (3.6, 4.6)	13	6.6 (3.5, 11.3)	12	8.6 (4.4, 15.0)	25	7.4 (4.8, 11.0)
Brain neoplasms	1	0.0 (0.0, 0.1)	2	0.1 (0.0, 0.2)	3	0.0 (0.0, 0.1)	1	0.5 (0.0, 2.8)	0	0.0 (0.0, 2.6)	1	0.3 (0.0, 1.7)
Glioblastoma	1	0.0 (0.0, 0.1)	0	0.0 (0.0, 0.1)	1	0.0 (0.0, 0.1)	1	0.5 (0.0, 2.8)	0	0.0 (0.0, 2.6)	1	0.3 (0.0, 1.7)
Other brain neoplasm	0	0.0 (0.0, 0.1)	2	0.1 (0.0, 0.2)	2	0.0 (0.0, 0.1)	0	0.0 (0.0, 1.9)	0	0.0 (0.0, 2.6)	0	0.0 (0.0, 1.1)
Pregnancy	**N/A**	**N/A**	**210**	**17.0 (14.8, 19.5)**	**210**	**17.0 (14.8, 19.5)**	**N/A**	**N/A**	**5**	**7.9 (2.6, 18.5)**	**5**	**7.9 (2.6, 18.5)**

Event	Conventional (n=6,343)						Benepali (n=451)					
	Males		Females		Total		Males		Females		Total	
	Events	IR/1,000PY (95% CI)	Events	IR/1,000 PY (95% CI)	Events	IR/1,000PY (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)	Events	IR/1,000 (95% CI)
Death	178	4.7 (4.1, 5.5)	101	3.5 (2.8, 4.2)	279	4.2 (3.7, 4.7)	3	3.2 (0.7, 9.2)	6	9.2 (3.4, 20.1)	9	5.6 (2.6, 10.7)

IR/1,000 = incidence rate per 1000 person years; 95% CI = 95% confidence interval; CHF = congestive heart failure; CNS = central nervous system; TB = tuberculosis; SAE = serious adverse event; N/A = Not Applicable.

Table 5. Number and rates of first events including unadjusted and adjusted hazard ratios per 1,000 person years

Serious Adverse Events	Conventional [N=6,343]		Benepali [N=451]		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	N	IR/1,000 (95% CI)	N	IR/1,000 (95% CI)		
Total Serious Infection	**612**	**9.63 (8.89, 10.42)**	**27**	**8.33 (5.72, 12.15)**	**0.78 (0.53, 1.14)**	**0.74 (0.50, 1.09)**
Pneumonia	200	2.98 (2.59, 3.42)	8	2.42 (1.21, 4.85)	0.75 (0.37, 1.52)	0.63 (0.31, 1.29)
Septicaemia	92	1.35 (1.10, 1.66)	1	0.30 (0.04, 2.14)	0.21 (0.03, 1.53)	0.19 (0.03, 1.36)
Bone/Joint infection	16	0.23 (0.14, 0.38)	0	0	N/A	N/A
Opportunistic infection	6	0.09 (0.04, 0.19)	0	0	N/A	N/A
Soft tissue and skin infection	144	2.13 (1.81, 2.51)	8	2.43 (1.21, 4.85)	1.00 (0.49, 2.05)	1.06 (0.51, 2.18)
Cellulitis	87	1.28 (1.04, 1.58)	3	0.90 (0.29, 2.80)	0.63 (0.20, 1.98)	0.64 (0.20, 2.06)
Other soft tissue and skin infection	71	1.04 (0.83, 1.31)	5	1.51 (0.63, 3.63)	1.29 (0.52, 3.20)	1.46 (0.58, 3.67)
Other serious infection	325	4.92 (4.42, 5.49)	14	4.27 (2.53, 7.21)	0.78 (0.46, 1.33)	0.76 (0.44, 1.32)
TB	**1**	**0.01 (0.00, 0.10)**	**0**	**0**	N/A	N/A
Respiratory (non-infection)	**101**	**1.49 (1.22, 1.81)**	**10**	**3.04 (1.64, 5.65)**	**1.81 (0.95, 3.47)**	**1.60 (0.82, 3.11)**
Cardiac SAE	**250**	**3.75 (3.31, 4.24)**	**15**	**4.56 (2.75, 7.56)**	**1.11 (0.66, 1.86)**	**0.99 (0.58, 1.68)**
CHF (new or worsening)	46	0.67 (0.50, 0.90)	3	0.90 (0.29, 2.80)	1.29 (0.40, 4.16)	1.03 (0.31, 3.38)
Myocardial infarction	94	1.38 (1.13, 1.69)	3	0.90 (0.29, 2.80)	0.60 (0.19, 1.90)	0.56 (0.18, 1.80)
Other cardiac events	154	2.28 (1.95, 2.67)	11	3.33 (1.85, 6.02)	1.31 (0.71, 2.41)	1.24 (0.66, 2.31)
Nervous System SAE	**174**	**2.58 (2.23, 3.00)**	**7**	**2.11 (1.01, 4.43)**	**0.76 (0.36, 1.62)**	**0.67 (0.31, 1.44)**
Central Demyelination	0	0	0	0	N/A	N/A
Peripheral neuropathy	4	0.06 (0.02, 0.16)	0	0	N/A	N/A
Seizures	20	0.29 (0.19, 0.45)	0	0	N/A	N/A
Cerebrovascular Accident	89	1.31 (1.06, 1.61)	2	0.60 (0.15, 2.41)	0.43 (0.11, 1.76)	0.36 (0.09, 1.49)
Other CNS	80	1.17 (0.94, 1.46)	6	1.81 (0.81, 4.03)	1.47 (0.64, 3.38)	1.30 (0.56, 3.03)
Skin (non cancer)	**219**	**3.29 (2.89, 3.76)**	**2**	**0.60 (0.15, 2.41)**	**0.15 (0.04, 0.59)**	**0.15 (0.04, 0.60)**
Total haematologic events	**21**	**0.31 (0.20, 0.47)**	**0**	**0**	N/A	N/A

Serious Adverse Events	Conventional [N=6,343]		Benepali [N=451]		Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	N	IR/1,000 (95% CI)	N	IR/1,000 (95% CI)		
Aplastic anaemia	3	0.04 (0.01, 0.14)	0	0	N/A	N/A
Pancytopaenia	2	0.03 (0.01, 0.12)	0	0	N/A	N/A
Agranulocytosis	1	0.01 (0.00, 0.10)	0	0	N/A	N/A
Other dyscrasia	16	0.23 (0.14, 0.38)	0	0	N/A	N/A
Total malignant events	**322**	**4.87 (4.37, 5.44)**	**36**	**7.15 (5.15, 9.91)**	**1.49 (1.06, 2.11)**	**1.17 (0.83, 1.67)**
Lymphoproliferative	22	0.32 (0.21, 0.49)	0	0	N/A	N/A
Lymphoma	15	0.22 (0.13, 0.36)	0	0	N/A	N/A
Myeloma	3	0.04 (0.01, 0.14)	0	0	N/A	N/A
Leukaemia	4	0.06 (0.02, 0.16)	0	0	N/A	N/A
Skin Cancer	114	1.68 (1.40, 2.02)	16	3.12 (1.91, 5.09)	1.89 (1.12, 3.18)	1.28 (0.75, 2.18)
Non Melanoma Skin Cancer	99	1.46 (1.20, 1.77)	15	2.92 (1.76, 4.84)	2.03 (1.18, 3.50)	1.38 (0.79, 2.40)
Melanoma	15	0.22 (0.13, 0.36)	1	0.19 (0.03, 1.36)	0.91 (0.12, 6.90)	0.66 (0.08, 5.10)
Other Skin Cancer	2	0.03 (0.01, 0.12)	1	0.19 (0.03, 1.36)	6.63 (0.60 – 73.2)	3.61 (0.32, 41.37)
Solid tumours	204	3.04 (2.65, 3.48)	20	3.91 (2.52, 6.06)	1.32 (0.83, 2.08)	1.12 (0.70, 1.79)
Brain neoplasms	3	0.04 (0.01, 0.14)	1	0.19 (0.03, 1.36)	4.13 (0.43, 39.76)	3.16 (0.29, 34.48)
Glioblastoma	1	0.01 (0.00, 0.10)	1	0.19 (0.03, 1.36)	12.38 (0.77 – 198.25)	5.71 (0.34, 96.67)
Other brain neoplasm	2	0.03 (0.01, 0.12)	0	0	N/A	N/A
Pregnancy	**181**	**2.69 (2.33, 3.12)**	**4**	**1.21 (0.45, 3.22)**	**0.39 (0.14, 1.04)**	**0.66 (0.24, 1.80)**
Death	**279**	**4.17 (3.71, 4.69)**	**9**	**2.71 (1.41, 5.21)**	**0.65 (0.34, 1.27)**	**0.56 (0.28, 1.09)**

IR/1000 = incidence rate per 1000 person years; 95% CI = 95% confidence interval; CHF = congestive heart failure; CNS = central nervous system; TB = tuberculosis; SAE = serious adverse event; N/A = Not applicable.

10.5 Other analyses

Not applicable.

10.6 Adverse events

The occurrence of adverse events in special interest within the treatment groups are described in section 10.4. Based on the SAE reports and non-serious events provided by the BADBIR Registry, a tabulation of events reported to the MAH broken down by SOC and PT is provided in the Table 6. It is to be noted that the categorization of events in BADBIR does not strictly adhere to the MedDRA SOC categorization. Therefore, the numbers presented in Table 6 and the other tables may not align.

Table 6. Tabulation of Reported Events

Primary SOC	Preferred Term	Seriousness		Total
		Yes	No	
Infections and infestations	Anal abscess	2	0	2
	Appendicitis	1	0	1
	Candida infection	0	1	1
	Cellulitis	4	0	4
	COVID-19	0	3	3
	Haematoma infection	1	0	1
	Herpes zoster	1	0	1
	Infected skin ulcer	1	0	1
	Infective exacerbation of chronic obstructive airways disease	1	0	1
	Lower respiratory tract infection	4	0	4
	Mycoplasma infection	1	0	1
	Nasal vestibulitis	0	1	1
	Nasopharyngitis	0	1	1
	Pneumonia	5	0	5
	Postpartum sepsis	1	0	1
	Pyelonephritis	1	0	1
	Rectal abscess	1	0	1
	Sinusitis	0	1	1
	Tinea cruris	0	1	1
	Tonsillitis	1	0	1
	Tooth infection	0	2	2
	Upper respiratory tract infection	0	1	1
	Urinary tract infection	1	0	1
	Urinary tract infection fungal	1	0	1
	Viral infection	1	0	1
	Infections and infestations Total	**28**	**11**	**39**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma metastatic	1	0	1
	Adenocarcinoma of colon	1	0	1
	Basal cell carcinoma	8	0	8
	Bowen's disease	1	0	1
	Breast cancer metastatic	1	0	1
	Cervix carcinoma	1	0	1
	Endometrial cancer	1	0	1
	Intraductal proliferative breast lesion	1	0	1
	Invasive lobular breast carcinoma	1	0	1
	Lung cancer metastatic	1	0	1
	Metastases to liver	1	0	1
	Metastatic malignant melanoma	1	0	1
	Oesophageal carcinoma	1	0	1
	Pancreatic neoplasm	1	0	1
	Prostate cancer	2	0	2
	Prostate cancer metastatic	1	0	1
	Skin cancer	1	0	1

Primary SOC	Preferred Term	Seriousness		Total
		Yes	No	
	Squamous cell carcinoma	12	0	12
	Squamous cell carcinoma of head and neck	1	0	1
	Triple negative breast cancer	1	0	1
	Urethral cancer	1	0	1
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) Total	**40**	**0**	**40**
Blood and lymphatic system disorders	Abdominal lymphadenopathy	0	1	1
	Iron deficiency anaemia	1	0	1
	Lymphadenopathy	0	1	1
	Blood and lymphatic system disorders Total	**1**	**2**	**3**
Immune system disorders	Hypersensitivity	0	1	1
	Immune system disorders Total	**0**	**1**	**1**
Metabolism and nutrition disorders	Hyperglycaemia	1	0	1
	Hypokalaemia	1	0	1
	Obesity	1	0	1
	Metabolism and nutrition disorders Total	**3**	**0**	**3**
Psychiatric disorders	Behaviour disorder	1	0	1
	Confusional state	1	0	1
	Mental disorder	1	0	1
	Sleep disorder	0	1	1
	Tobacco abuse	1	0	1
	Psychiatric disorders Total	**4**	**1**	**5**
Nervous system disorders	Amnesia	1	0	1
	Carotid artery stenosis	1	0	1
	Dizziness	0	1	1
	Nervous system disorders Total	**2**	**1**	**3**
Eye disorders	Vision blurred	0	1	1
	Eye disorders Total	**0**	**1**	**1**
Ear and labyrinth disorders	Ear swelling	0	1	1
	Ear and labyrinth disorders Total	**0**	**1**	**1**
Cardiac disorders	Acute myocardial infarction	2	0	2
	Aortic valve stenosis	1	0	1
	Atrial fibrillation	3	0	3
	Atrial flutter	2	0	2
	Cardiac failure	1	0	1
	Cardiac failure congestive	1	0	1
	Supraventricular tachycardia	1	0	1
	Cardiac disorders Total	**11**	**0**	**11**
Vascular disorders	Essential hypertension	1	1	2
	Haematoma	1	0	1
	Haemorrhage	1	0	1
	Vascular disorders Total	**3**	**1**	**4**
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	0	1
	Epistaxis	1	1	2
	Hypoventilation neonatal	1	0	1

Primary SOC	Preferred Term	Seriousness		Total
		Yes	No	
	Oropharyngeal pain	0	1	1
	Pleural effusion	1	0	1
	Pneumothorax	1	0	1
	Productive cough	0	1	1
	Pulmonary fibrosis	1	0	1
	Respiratory failure	1	0	1
	Tonsillar hypertrophy	0	1	1
	Respiratory, thoracic and mediastinal disorders Total	**7**	**4**	**11**
Gastrointestinal disorders	Anal fissure	0	1	1
	Anal fistula	1	0	1
	Anogenital dysplasia	1	0	1
	Colitis ulcerative	1	0	1
	Diverticulum	1	0	1
	Haemorrhoids	0	1	1
	Pancreatitis	2	0	2
	Tongue dysplasia	1	0	1
	Gastrointestinal disorders Total	**7**	**2**	**9**
Hepatobiliary disorders	Cholecystitis	1	0	1
	Hepatobiliary disorders Total	**1**	**0**	**1**
Skin and subcutaneous tissue disorders	Actinic keratosis	0	1	1
	Blister	0	1	1
	Dermatitis exfoliative generalised	1	0	1
	Erythema	0	1	1
	Erythrodermic psoriasis	1	0	1
	Night sweats	0	1	1
	Psoriasis	0	5	5
	Rash	0	1	1
	Urticaria	0	1	1
	Skin and subcutaneous tissue disorders Total	**2**	**11**	**13**
Musculoskeletal and connective tissue disorders	Arthralgia	0	1	1
	Exostosis	1	0	1
	Foot deformity	1	0	1
	Osteoarthritis	1	1	2
	Pain in extremity	0	1	1
	Psoriatic arthropathy	1	0	1
	Musculoskeletal and connective tissue disorders Total	**4**	**3**	**7**
Renal and urinary disorders	Acute kidney injury	2	0	2
	Chronic kidney disease	3	0	3
	End stage renal disease	1	0	1
	Micturition urgency	0	1	1
	Nephrolithiasis	1	0	1
	Renal and urinary disorders Total	**7**	**1**	**8**
	Gestational diabetes	1	0	1

Primary SOC	Preferred Term	Seriousness		Total
		Yes	No	
Pregnancy, puerperium and perinatal conditions	Premature baby	1	0	1
	Pregnancy, puerperium and perinatal conditions Total	**2**	**0**	**2**
Reproductive system and breast disorders	Uterine enlargement	1	0	1
	Vaginal haemorrhage	1	0	1
	Reproductive system and breast disorders Total	**2**	**0**	**2**
Congenital, familial and genetic disorders	Congenital eye disorder	1	0	1
	Heart block congenital	1	0	1
	Congenital, familial and genetic disorders Total	**2**	**0**	**2**
General disorders and administration site conditions	Catheter site erythema	1	0	1
	Chest discomfort	0	1	1
	Chest pain	1	0	1
	Cyst	1	0	1
	Feeling hot	0	2	2
	Influenza like illness	0	2	2
	Injection site discharge	0	1	1
	Injection site pain	0	1	1
	Pyrexia	0	1	1
	Swelling	0	1	1
	Therapeutic product effect incomplete	0	1	1
	General disorders and administration site conditions Total	**3**	**10**	**13**
Investigations	Alanine aminotransferase increased	1	0	1
	Blood test abnormal	1	0	1
	Escherichia test positive	1	0	1
	Investigations Total	**3**	**0**	**3**
Injury, poisoning and procedural complications	Contusion	0	1	1
	Exposure via breast milk	0	1	1
	Foetal exposure during pregnancy	1	0	1
	Maternal exposure before pregnancy	1	0	1
	Maternal exposure during pregnancy	0	1	1
	Off label use	0	4	4
	Product use issue	0	4	4
	Injury, poisoning and procedural complications Total	**2**	**11**	**13**
Surgical and medical procedures	Angioplasty	1	0	1
	Cardiac pacemaker insertion	1	0	1
	Hip arthroplasty	1	0	1
	Hospitalisation	1	0	1
	Surgical and medical procedures Total	**4**	**0**	**4**
Product issues	Product substitution issue	0	1	1
	Product issues Total	**0**	**1**	**1**
Total Number of Events		**138**	**62**	**200**

11 Discussion

11.1 Key results

BADBIR is a prospective observational cohort study with the primary aim to monitor the long-term safety of biologic interventions for psoriasis. Since the issuance of marketing authorisation for Benepali on 14 Jan 2016, BADBIR started recruitment of patients with psoriasis starting Benepali. Overall, as of 31 July 2025, 451 patients have registered into the Benepali cohort, comprising 122 newly registered patients and 329 patients who switched to Benepali from another biologic therapy.

This report describes baseline characteristics and long-term outcomes of patients with psoriasis treated with Benepali compared to conventional systemic therapies. The analysis included 6,343 patients in the conventional cohort and 451 patients in the Benepali cohort.

At baseline, differences were observed in the characteristics between the two cohorts. Patients in the Benepali cohort were older and had longer disease duration compared to the conventional cohort. Conversely, patients in the conventional cohort had higher disease activity at baseline, with higher PASI scores and DLQI scores.

In terms of safety, the rate of overall serious adverse events was comparable between the two cohorts. Among the key serious adverse events monitored, both groups showed the highest incidence in Total Serious Infection, in line with previous studies. No TB or haematologic events were reported in the Benepali group during the study. Additionally, no cases of lymphoproliferative disease, lymphoma, myeloma, or leukaemia were observed in the Benepali cohort. Notably, Skin (non-cancer) events showed a significantly lower risk in the Benepali group, with an adjusted HR of 0.15 (95% CI: 0.04-0.60); however, given that only 2 events were reported in the Benepali cohort, caution should be exercised in interpretation.

For Total Malignant Events, the Benepali group showed a higher crude incidence rate compared to the conventional group; however, the adjusted HR was 1.17 (95% CI: 0.83-1.67), indicating no statistically significant difference after adjustment for confounders. This was primarily driven by elevated rates of Skin Cancer and Solid Tumour.

In conclusion, no new safety signals were identified with the use of Benepali in psoriasis patients. The benefit-risk profile of Benepali remains positive.

11.2 Limitations

The data are observational and collected from dermatology centres across the UK and ROI as direct reports into the study. Common challenges such as missing data are recognised and where applicable, multiple imputation has been used to minimise the impact of this. There are several limitations specific to this report.

First, this is an observational study design, and differences in baseline characteristics existed between the two cohorts. The Benepali cohort had a higher mean age and longer disease duration, as well as a higher proportion of patients with previous UV therapy. Although propensity score adjustment was performed, residual confounding may still exist from unmeasured factors.

Second, the Benepali cohort (n=451) was substantially smaller than the conventional cohort (n=6,343), which may limit statistical power for detecting differences in rare adverse events. This resulted in insufficient event counts for some analyses, making comparisons impossible for certain outcomes.

Third, a substantial proportion of patients in the Benepali cohort had switched from other biologic therapies (329 patients, 73%) rather than being newly registered (122 patients, 27%). This may introduce

a "healthy user effect," as patients who tolerated previous biologic therapies well may be more likely to switch to Benepali, potentially biasing safety outcomes favourably.

Lastly, data collection relies on direct reporting from clinical sites, and some adverse events may have been missed or under-reported.

11.3 Interpretation

This study evaluated the long-term safety of Benepali in UK and ROI patients with psoriasis using BADBIR registry data. The study results showed that long-term treatment with Benepali is well-tolerated. The pattern and frequency of key safety outcomes were generally consistent with the established safety profile of Benepali. The incidence rate of Total Serious Infection showed a numerically lower trend in the Benepali group (adjusted HR 0.74, 95% CI: 0.50-1.09), although this was not statistically significant. This is consistent with the known safety profile of etanercept.

Regarding malignancy, although the crude incidence rate was higher in the Benepali group, the adjusted HR showed no statistically significant difference. This finding reflects the baseline characteristics differences, particularly the higher age, longer disease duration, and greater proportion of previous UV therapy exposure in the Benepali cohort. Notably, previous UV therapy is a well-established risk factor for non-melanoma skin cancer. The absence of TB, haematologic events, and lymphoproliferative disorders in the Benepali cohort is reassuring; however, caution is needed in interpreting this as definitive safety evidence given the limited sample size.

11.4 Generalisability

Considering that this study utilised data from BADBIR which collects data from patients with psoriasis in the UK and ROI, the analysis results in this report may have limitations in being extrapolated to the general global population. Particularly, generalisability to other healthcare systems and regions with different patient demographics, treatment practices, and ethnic compositions may be limited.

However, this study presents organised data in psoriasis patients based on a prospective observational study, providing evidence for Benepali's safety profile based on real-world data. The prospective design and standardised data collection methods enhance the reliability of the findings.

12 Other information

None.

13 Conclusion

Benepali was well-tolerated in patients with psoriasis, considering that the risk of safety concerns associated with Benepali use was not observed to be significantly higher compared to conventional systemic therapies. Analyses of BADBIR data demonstrated the tolerable safety profile of Benepali in the psoriasis population. In addition, there was no novel safety finding to change the current benefit-risk balance of Benepali during the study. The benefit-risk profile of Benepali remains positive for use in the approved indication.

14 References

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