CLINICAL STUDY REPORT

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Brexiprant in Patients with Moderate-to-Severe Plaque Psoriasis

Protocol BREX-301

EudraCT Number: 2024–001234–56
IND Number: 123,456
NCT Number: NCT06123456

Sponsor:
Valkyra Bio Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936, USA

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Synopsis

Study Identification

Name of Sponsor	Valkyra Bio Pharmaceuticals Corporation
Name of Finished Product	Brexiprant (film-coated tablet)
Name of Active Ingredient	Brexiprant
Study Title	A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Brexiprant in Patients with Moderate-to-Severe Plaque Psoriasis
Protocol Number	BREX-301
EudraCT Number	2024–001234–56
NCT Number	NCT06123456
Phase of Development	Phase III

Methodology

Study Design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Patients were randomized in a 2:1 ratio to receive either Brexiprant 300 mg or placebo once daily for 52 weeks. The study comprised a 4-week screening period, a 52-week treatment period, and a 4-week follow-up period.
Number of Patients	
Planned	A total of 660 patients (440 Brexiprant, 220 placebo)
Enrolled	950 patients were screened; 675 were randomized (Intent-to-Treat population)
Completed	590 patients (87.4%) completed the 52-week treatment period
Diagnosis and Main Criteria for Inclusion	Adult patients (18–75 years) with a diagnosis of moderate-to-severe chronic plaque psoriasis for ≥ 6 months, with a PASI score ≥ 12, a static Physician's Global Assessment (sPGA) score ≥ 3, and body surface area (BSA) involvement $\geq 10\%$ at screening and baseline.

Test Product, Dose, and Mode of Administration	Brexiprant 300 mg film-coated tablet, administered orally once daily.
Reference Therapy, Dose, and Mode of Administration	Matching placebo film-coated tablet, administered orally once daily.
Duration of Treatment	52 weeks

Evaluation Criteria

Primary Efficacy Endpoint	Proportion of patients achieving a $\geq 75\%$ reduction from baseline in Psoriasis Area and Severity Index (PASI 75) at Week 16.
Key Secondary Endpoints	1. Proportion of patients achieving sPGA score of 0 (clear) or 1 (almost clear) at Week 16. 2. Proportion of patients achieving PASI 90 at Week 16. 3. Change from baseline in Dermatology Life Quality Index (DLQI) at Week 16. 4. Proportion of patients achieving PASI 75 at Week 52.
Safety Endpoints	Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory parameters, vital signs, electrocardiograms, and physical examinations.
Pharmacokinetic Endpoints	Trough plasma concentrations of brexiprant at Weeks 4, 16, and 52 (subset of patients).

Statistical Methods

Primary Analysis	The primary efficacy analysis was performed on the Full Analysis Set (FAS) using a Cochran–Mantel–Haenszel (CMH) test stratified by baseline weight (≤ 90 kg vs. > 90 kg) and prior biologic use (yes/no).
Sample Size Determination	A sample size of 660 patients (440 Brexiprant, 220 placebo) provided $\geq 95\%$ power to detect a 25% absolute difference in PASI 75 response rates at Week 16, assuming a placebo response rate of 15% and a two-sided significance level of 0.05, accounting for a 15% dropout rate.
Multiplicity Adjustment	A hierarchical testing procedure was applied to control the family-wise Type I error rate across the primary and key secondary endpoints.
Interim Analyses	One pre-planned interim analysis for futility was conducted by an independent Data Safety Monitoring Board (DSMB) when 50% of patients completed Week 16.

Summary of Results

Efficacy	**Primary Endpoint Met:** The proportion of patients achieving PASI 75 at Week 16 was 72.3% in the Brexiprant group versus 14.2% in the placebo group (adjusted difference: 58.1%; 95% CI: 52.4%, 63.8%; $p < 0.0001$). All key secondary endpoints were met with statistical significance ($p < 0.0001$).
Safety	Brexiprant was generally well tolerated over 52 weeks. The most frequently reported TEAEs in the Brexiprant group were nasopharyngitis (18.2%), upper respiratory tract infection (12.4%), and headache (8.9%). SAEs were reported in 4.2% of Brexiprant-treated patients and 3.6% of placebo-treated patients. No deaths occurred during the study.
Conclusion	Brexiprant 300 mg administered orally once daily demonstrated superior efficacy compared to placebo for the treatment of moderate-to-severe plaque psoriasis, with a favorable safety profile consistent with the known mechanism of action.

Contents

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PASI 75	$\geq 75\%$ Reduction from Baseline in PASI Score
PASI 90	$\geq 90\%$ Reduction from Baseline in PASI Score
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
sPGA	Static Physician's Global Assessment
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal

1 Ethics

1.1 Independent Ethics Committee / Institutional Review Board

This study was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable local regulatory requirements. The study protocol, all protocol amendments, the Investigator's Brochure, the informed consent forms, and any other relevant study documents were reviewed and approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each participating site prior to the enrollment of patients. A list of all IECs/IRBs that reviewed the study is provided in Appendix 16.1.1.

The study protocol (Version 3.0, dated 12 February 2025) and two subsequent amendments (Amendment 1: 03 June 2025; Amendment 2: 18 October 2025) received favorable opinion from all relevant ethics committees before implementation.

1.2 Ethical Conduct of the Study

Written informed consent was obtained from each patient before any study-related procedures were performed. Patients were provided with both verbal and written information regarding the nature, purpose, potential risks, and benefits of the study, and were given sufficient time to consider their participation. The informed consent process was documented in each patient's medical record.

1.3 Patient Information and Consent

The informed consent form included a separate section for optional genetic sampling and long-term storage of biological specimens for future exploratory biomarker research. Patients who declined genetic testing were still eligible for participation in the main study.

2 Investigators and Study Administrative Structure

2.1 Principal and Coordinating Investigators

The study was conducted under the direction of the following key investigators:

Steering Committee Chair	Prof. Elena Vasquez, MD, PhD — Department of Dermatology, University of Barcelona, Spain
Coordinating Principal Investigator	Dr. Marcus Chen, MD — Icahn School of Medicine at Mount Sinai, New York, NY, USA
Medical Expert	Dr. Sanjay Patel, MD, FRCP — St. John's Institute of Dermatology, London, UK
Biostatistics Lead	Dr. Yuki Tanaka, PhD — Valkyra Bio Pharma AG, Basel, Switzerland

2.2 Study Centers

The study was conducted at 78 sites across 12 countries in North America, Europe, and Asia-Pacific. A total of 675 patients were randomized across 62 active sites. The complete list of investigators and study centers is provided in Appendix 16.1.4.

2.3 Sponsor Oversight

The sponsor, Valkyra Bio Pharmaceuticals Corporation, was responsible for study design, monitoring, data management, statistical analysis, and reporting. An independent Contract Research Organization (CRO), IQVIA, was contracted to perform on-site monitoring, data management, and certain pharmacovigilance activities. An independent Data Safety Monitoring Board (DSMB) provided oversight of patient safety.

3 Introduction

Plaque psoriasis is a chronic, immune-mediated inflammatory skin disease affecting approximately 2–3% of the global population. The condition is characterized by well-demarcated, erythematous, scaly plaques that can cause significant physical discomfort, psychological distress, and impairment in quality of life. Moderate-to-severe disease, defined as involvement of $\geq 10\%$ body surface area or a Psoriasis Area and Severity Index (PASI) score ≥ 12, typically requires systemic therapy.

Despite advances in biologic therapies targeting tumor necrosis factor (TNF), interleukin-17 (IL-17), and interleukin-23 (IL-23), a significant proportion of patients either fail to achieve adequate disease control or lose response over time. Furthermore, the parenteral route of administration for all currently approved biologics represents a barrier for patients who prefer oral therapy.

Brexiprant is a novel, orally bioavailable, small-molecule allosteric modulator of the receptor-type tyrosine-protein phosphatase SHP-2 (encoded by the *PTPN11* gene), which acts upstream of the IL-23/Th17 axis—a pathway central to the pathogenesis of plaque psoriasis. Nonclinical studies demonstrated that brexiprant selectively inhibits Th17 cell differentiation and expansion, leading to reduced production of IL-17A, IL-17F, and IL-22. Phase I and Phase II clinical studies established the pharmacokinetic profile, safety, and preliminary efficacy of brexiprant in patients with moderate-to-severe plaque psoriasis.

The present Phase III study (BREX-301) was designed to confirm the efficacy and safety of brexiprant 300 mg administered orally once daily compared to placebo over a 52-week treatment period in adults with moderate-to-severe plaque psoriasis. This report presents the final results of the study in accordance with the ICH E3 Guideline on the Structure and Content of Clinical Study Reports.

4 Study Objectives

4.1 Primary Objective

The primary objective of this study was to evaluate the efficacy of Brexiprant 300 mg administered orally once daily compared to placebo in the treatment of adults with moderate-to-severe plaque psoriasis, as measured by the proportion of patients achieving a $\geq 75\%$ reduction from baseline in Psoriasis Area and Severity Index (PASI 75) at Week 16.

4.2 Secondary Objectives

The secondary objectives were to evaluate the efficacy of Brexiprant compared to placebo with respect to:

1. Proportion of patients achieving a static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) at Week 16.
2. Proportion of patients achieving PASI 90 at Week 16.
3. Change from baseline in Dermatology Life Quality Index (DLQI) at Week 16.
4. Long-term maintenance of response (PASI 75 at Week 52).

4.3 Safety Objective

To evaluate the safety and tolerability of Brexiprant 300 mg administered orally once daily for up to 52 weeks, including the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), changes in clinical laboratory parameters, vital signs, and electrocardiogram findings.

4.4 Pharmacokinetic Objective

To characterize the trough plasma concentration (C_{trough}) of brexiprant in a subset of patients at Weeks 4, 16, and 52.

5 Investigational Plan

5.1 Overall Study Design and Plan

Study BREX-301 was a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. The overall study design is illustrated in Figure 1.

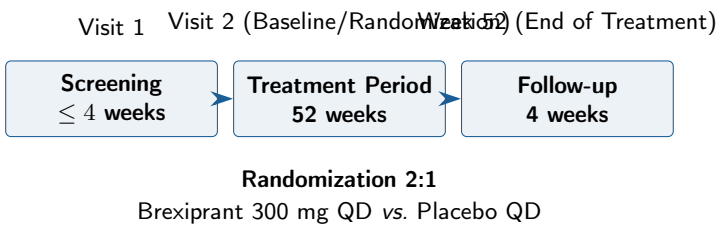

Figure 1. Overall Study Design

The study consisted of three periods: (1) a screening period of up to 4 weeks (Visits 1–2), during which patients were assessed for eligibility; (2) a 52-week double-blind treatment period (Visits 2–18), during which patients received either Brexiprant 300 mg or matching placebo once daily (QD); and (3) a 4-week post-treatment follow-up period (Visit 19). Study visits occurred at Weeks 0 (Baseline), 2, 4, 8, 12, 16, 24, 32, 40, and 52 during the treatment period.

Randomization was stratified by baseline weight category (≤ 90 kg vs. > 90 kg) and prior biologic use for psoriasis (yes/no). An Interactive Response Technology (IRT) system was used to assign patients to treatment groups.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

Patients were eligible for enrollment if they met all of the following criteria:

- Male or female, aged 18 to 75 years at the time of screening.
- Diagnosis of moderate-to-severe chronic plaque psoriasis for at least 6 months prior to screening.
- PASI score ≥ 12 at both screening and baseline visits.
- sPGA score ≥ 3 (moderate) at both screening and baseline visits.
- BSA involvement $\geq 10\%$ at both screening and baseline visits.
- Candidate for systemic therapy or phototherapy for psoriasis.
- Body weight ≥ 40 kg and BMI ≤ 40 kg/m^2.
- Able to provide written informed consent.

5.2.2 Exclusion Criteria

Key exclusion criteria included: non-plaque forms of psoriasis (guttate, erythrodermic, pustular); prior exposure to brexiprant; use of any biologic therapy within 5 half-lives or 12 weeks (whichever was longer) prior to baseline; use of systemic non-biologic psoriasis therapy within 4 weeks of baseline; active or latent tuberculosis; history of malignancy within 5 years (except treated non-melanoma skin cancer); clinically significant laboratory abnormalities at screening; pregnant or lactating women; and active infection requiring systemic antimicrobial therapy within 2 weeks of baseline.

5.3 Treatments

5.3.1 Investigational Product

Brexiprant was supplied as 300 mg film-coated tablets for oral administration. The dosage was one tablet taken orally once daily with water, with or without food, at approximately the same time each day. The 300 mg dose was selected based on the Phase II dose-ranging study (BREX-201), which demonstrated maximal efficacy at this dose with a favorable benefit–risk profile.

5.3.2 Reference Therapy

Matching placebo tablets, identical in appearance, size, and packaging to the active treatment, were administered orally once daily.

5.3.3 Concomitant Therapy

Low-to-moderate potency topical corticosteroids (Class III–VII) were permitted for treatment of the face, axillae, and groin throughout the study at the investigator's discretion. Emollients and moisturizers were allowed on all body areas except within 12 hours of a study visit. All other psoriasis therapies (topical, systemic, phototherapy) were prohibited during the study.

5.4 Efficacy and Safety Variables

The efficacy assessments included PASI scores, sPGA scores, DLQI scores, and BSA involvement at each study visit. Safety assessments included monitoring of treatment-emergent adverse events (TEAEs) using MedDRA version 27.0 coding, serious adverse events (SAEs), clinical laboratory evaluations (hematology, clinical chemistry, urinalysis), vital signs, 12-lead electrocardiograms, and physical examinations. TEAEs were defined as AEs with onset on or after the date of the first dose of study drug through 30 days after the last dose.

5.5 Statistical Methods

The Full Analysis Set (FAS) comprised all randomized patients who received at least one dose of study drug and had at least one post-baseline PASI assessment. The Per-Protocol (PP) analysis set included all FAS patients without major protocol deviations. The Safety Set included all randomized patients who received at least one dose of study drug.

The primary efficacy analysis compared the proportion of patients achieving PASI 75 at Week 16 between treatment groups using a Cochran–Mantel–Haenszel (CMH) test stratified by baseline weight category (≤ 90 kg vs. > 90 kg) and prior biologic use (yes/no). Missing data were imputed using non-responder imputation (NRI) for the primary analysis. Sensitivity analyses using multiple imputation (MI) and tipping-point analyses were pre-specified.

A hierarchical testing procedure was applied to control the family-wise Type I error rate for the secondary endpoints, tested in the following pre-specified order: (1) sPGA 0/1 at Week 16, (2) PASI 90 at Week 16, (3) DLQI change from baseline at Week 16, and (4) PASI 75 at Week 52.

The statistical analysis plan (SAP) was finalized on 15 July 2025, prior to database lock and unblinding. A cross-reference between the SAP and this CSR is provided in Section 10.

6 Study Patients

6.1 Disposition of Patients

A total of 950 patients were screened at 78 study sites across 12 countries. Of these, 675 patients (71.1%) met all eligibility criteria and were randomized in a 2:1 ratio to receive Brexiprant 300 mg ($N = 450$) or placebo ($N = 225$). The most common reasons for screen failure were failure to meet PASI or sPGA severity thresholds (42.5%), exclusionary laboratory findings (18.2%), and withdrawal of consent (13.8%).

The patient disposition is summarized in Table 2 and illustrated in Figure 2.

Table 2. Patient Disposition (All Randomized Patients)

	Brexiprant 300 mg ($N = 450$)	Placebo ($N = 225$)	Total ($N = 675$)
Randomized	450 (100.0%)	225 (100.0%)	675 (100.0%)
Treated ($\geq$ 1 dose)	448 (99.6%)	224 (99.6%)	672 (99.6%)
Completed Week 16	418 (92.9%)	202 (89.8%)	620 (91.9%)
Completed Week 52	398 (88.4%)	192 (85.3%)	590 (87.4%)
Primary Reason for Discontinuation (by Week 52)			
Adverse Event	18 (4.0%)	6 (2.7%)	24 (3.6%)
Lack of Efficacy	8 (1.8%)	14 (6.2%)	22 (3.3%)
Withdrawal by Subject	14 (3.1%)	8 (3.6%)	22 (3.3%)
Lost to Follow-up	6 (1.3%)	3 (1.3%)	9 (1.3%)
Protocol Deviation	3 (0.7%)	1 (0.4%)	4 (0.6%)
Other	3 (0.7%)	1 (0.4%)	4 (0.6%)

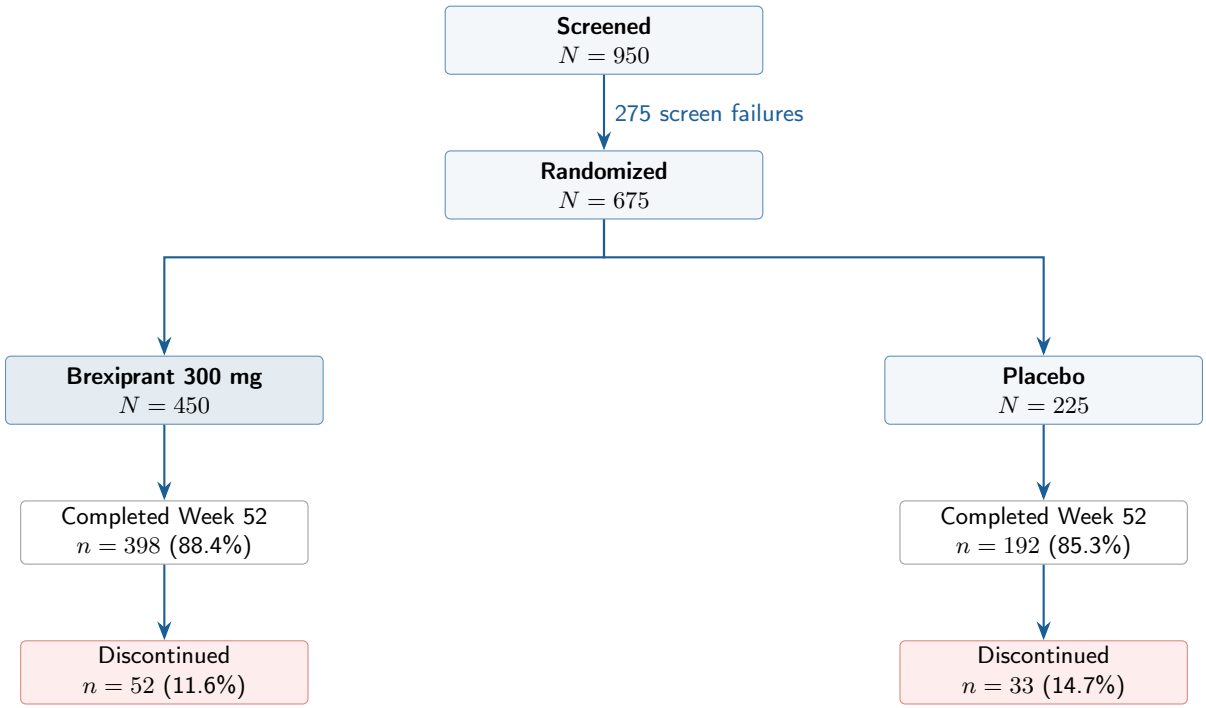

Figure 2. Patient Disposition Flowchart

6.2 Protocol Deviations

A total of 127 protocol deviations were reported among 94 patients (13.9% of the randomized population). The most frequent deviations were related to visit scheduling outside the protocol-specified window (58 events; 8.6% of patients), followed by missed study drug doses for 3 or more consecutive days (27 events; 4.0% of patients). Major protocol deviations that led to exclusion from the Per-Protocol (PP) analysis set were identified in 42 patients (6.2%), most commonly due to use of prohibited concomitant medication ($n = 18$) and non-compliance with study drug ($n = 14$).

All protocol deviations were reviewed by the study team and the sponsor prior to database lock. No individual protocol deviation was considered to have materially affected the integrity of the study results.

7 Efficacy Evaluation

7.1 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics were well balanced between treatment groups (Table 3). The mean age was 44.3 years, 62.8% of patients were male, and the mean baseline PASI score was 20.4. Approximately 28.1% of patients had prior biologic exposure for psoriasis.

Table 3. Demographic and Baseline Characteristics (Full Analysis Set)

	Brexiprant 300 mg ($N = 447$)	**Placebo ($N = 223$)**	**Total ($N = 670$)**
Age (years), mean ± SD	44.1 ± 13.2	44.7 ± 12.9	44.3 ± 13.1
Age (years), median (range)	43 (18–75)	45 (19–74)	44 (18–75)
Male, n (%)	283 (63.3%)	138 (61.9%)	421 (62.8%)
Race, n (%)			
White	366 (81.9%)	184 (82.5%)	550 (82.1%)
Black or African American	38 (8.5%)	17 (7.6%)	55 (8.2%)
Asian	31 (6.9%)	16 (7.2%)	47 (7.0%)
Other	12 (2.7%)	6 (2.7%)	18 (2.7%)
Weight (kg), mean ± SD	83.7 ± 18.4	84.1 ± 17.8	83.8 ± 18.2
BMI (kg/m^2), mean ± SD	28.6 ± 6.1	28.9 ± 5.9	28.7 ± 6.0
Disease Characteristics			
Psoriasis duration (yr), mean ± SD	16.8 ± 11.3	17.2 ± 11.7	16.9 ± 11.4
PASI score, mean ± SD	20.5 ± 7.3	20.2 ± 7.1	20.4 ± 7.2
sPGA 3 (moderate), n (%)	313 (70.0%)	158 (70.9%)	471 (70.3%)
sPGA 4 (severe), n (%)	134 (30.0%)	65 (29.1%)	199 (29.7%)
BSA involvement (%), mean ± SD	28.3 ± 14.6	27.9 ± 14.2	28.2 ± 14.5
DLQI score, mean ± SD	14.2 ± 6.6	14.0 ± 6.4	14.1 ± 6.5
Prior biologic use, n (%)	127 (28.4%)	61 (27.4%)	188 (28.1%)

7.2 Primary Efficacy Endpoint

The primary efficacy endpoint was met (Table 4). At Week 16, the proportion of patients achieving PASI 75 was significantly greater in the Brexiprant group (72.3%) compared to the placebo group (14.2%), with an adjusted treatment difference of 58.1% (95% CI: 52.4%, 63.8%; $p < 0.0001$). The superiority of Brexiprant over placebo was consistent across all pre-specified subgroups defined by baseline weight, prior biologic use, sex, age, race, and geographic region.

Table 4. Primary Efficacy Endpoint: PASI 75 Response at Week 16 (FAS, NRI)

	Brexiprant 300 mg ($N = 447$)	**Placebo ($N = 223$)**	**Treatment Difference (95% CI)**
PASI 75 responders, *n* (%)	323 (72.3)	31 (14.2)	—
Adjusted difference, %	—	—	58.1 (52.4, 63.8)
CMH test statistic		$Q_{\text{CMH}} = 198.4$	
p-value (two-sided)		$p < 0.0001$	

7.3 Key Secondary Efficacy Endpoints

All key secondary efficacy endpoints were met with statistical significance following the pre-specified hierarchical testing procedure (Table 5). The proportion of patients achieving sPGA 0/1 at Week 16 was 62.9% in the Brexiprant group compared to 9.0% in the placebo group ($p < 0.0001$). PASI 90 was achieved by 48.8% and 4.9% of patients in the Brexiprant and placebo groups, respectively ($p < 0.0001$). A clinically meaningful and statistically significant improvement in DLQI was observed in the Brexiprant group (LS mean change: -10.4) compared to placebo (-2.3; $p < 0.0001$).

Table 5. Key Secondary Efficacy Endpoints at Week 16 (FAS, NRI)

	Brexiprant 300 mg ($N = 447$)	**Placebo ($N = 223$)**	**Treatment Difference (95% CI); *p*-value**
sPGA 0/1, *n* (%)	281 (62.9)	20 (9.0)	53.9 (48.5, 59.3); $p < 0.0001$
PASI 90, *n* (%)	218 (48.8)	11 (4.9)	43.8 (38.7, 49.0); $p < 0.0001$
DLQI, LS mean change (SE)	-10.4 (0.3)	-2.3 (0.4)	-8.1 $(-9.1, -7.1)$; $p < 0.0001$
PASI 75 at Week 52, *n* (%)	336 (75.2)	—	Maintained; $p < 0.0001$[a]

[a] Compared to placebo PASI 75 response at Week 16 (14.2%).

8 Safety Evaluation

8.1 Extent of Exposure

The median duration of exposure to study drug was 356 days (range: 12–398 days) in the Brexiprant group and 350 days (range: 8–387 days) in the placebo group. Overall, 88.4% of patients in the Brexiprant group and 85.3% in the placebo group completed 52 weeks of treatment. The cumulative patient-years of exposure were 405.2 patient-years for Brexiprant and 196.8 patient-years for placebo.

8.2 Overview of Adverse Events

An overall summary of treatment-emergent adverse events is presented in Table 6. The proportion of patients reporting at least one TEAE was comparable between the Brexiprant group (62.5%) and the placebo group (58.9%). Most TEAEs were mild or moderate in severity (Grade 1 or 2 per CTCAE v5.0).

Table 6. Overall Summary of Treatment-Emergent Adverse Events (Safety Set)

	Brexiprant 300 mg ($N = 448$) *n* (%)	Placebo ($N = 224$) *n* (%)	Total ($N = 672$) *n* (%)
Any TEAE	280 (62.5)	132 (58.9)	412 (61.3)
Any drug-related TEAE[a]	148 (33.0)	54 (24.1)	202 (30.1)
Any TEAE Grade ≥ 3	22 (4.9)	10 (4.5)	32 (4.8)
Any SAE	19 (4.2)	8 (3.6)	27 (4.0)
Any TEAE leading to discontinuation	18 (4.0)	6 (2.7)	24 (3.6)
Death	0	0	0

[a] Assessed as possibly, probably, or definitely related to study drug by the investigator.

8.3 Adverse Events by System Organ Class and Preferred Term

Treatment-emergent adverse events categorized by System Organ Class (SOC) and Preferred Term (PT) occurring in $\geq 2\%$ of patients in either treatment group are summarized in Table 7. Events were coded using MedDRA version 27.0. The most frequently reported TEAEs by SOC were infections and infestations (34.6%), nervous system disorders (13.8%), and gastrointestinal disorders (15.2%).

Table 7. Treatment-Emergent Adverse Events by SOC and PT ($\geq$ 2% in Either Group; Safety Set)

System Organ Class / Preferred Term	Brexiprant 300 mg (N = 448) *n* (%)	Placebo (N = 224) *n* (%)	Total (N = 672) *n* (%)
Infections and Infestations			
Nasopharyngitis	81 (18.1)	33 (14.7)	114 (17.0)
Upper respiratory tract infection	56 (12.5)	21 (9.4)	77 (11.5)
Urinary tract infection	18 (4.0)	8 (3.6)	26 (3.9)
Sinusitis	14 (3.1)	6 (2.7)	20 (3.0)
Bronchitis	11 (2.5)	5 (2.2)	16 (2.4)
Nervous System Disorders			
Headache	40 (8.9)	18 (8.0)	58 (8.6)
Dizziness	11 (2.5)	5 (2.2)	16 (2.4)
Gastrointestinal Disorders			
Diarrhea	28 (6.3)	12 (5.4)	40 (6.0)
Nausea	22 (4.9)	10 (4.5)	32 (4.8)
Abdominal pain	13 (2.9)	7 (3.1)	20 (3.0)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	16 (3.6)	11 (4.9)	27 (4.0)
Back pain	15 (3.3)	8 (3.6)	23 (3.4)
Skin and Subcutaneous Tissue Disorders			
Pruritus	14 (3.1)	9 (4.0)	23 (3.4)
General Disorders and Administration Site Conditions			
Fatigue	18 (4.0)	10 (4.5)	28 (4.2)

8.4 Serious Adverse Events

Serious adverse events (SAEs) were reported in 19 patients (4.2%) in the Brexiprant group and 8 patients (3.6%) in the placebo group. No individual SAE preferred term was reported in more than one patient in either treatment group. The SAEs reported in the Brexiprant group included: appendicitis ($n = 1$), cholelithiasis ($n = 1$), pneumonia ($n = 2$), cellulitis ($n = 1$), transient ischemic attack ($n = 1$), non-ST elevation myocardial infarction ($n = 1$), and fractures secondary to accidental trauma ($n = 2$). None of the SAEs were assessed as related to study drug by the investigator.

No deaths occurred during the study treatment period. Two deaths were reported in the post-treatment follow-up period, both in the Brexiprant group: one due to a motor vehicle accident (Day 389, 25 days after the last dose) and one sudden death of unknown cause (Day 378, 14 days after the last dose). Both events were assessed by the investigator and the DSMB as unrelated to study drug.

8.5 DSMB Oversight

The independent Data Safety Monitoring Board (DSMB) met three times during the study (after 25%, 50%, and 75% of patients completed Week 16) to review unblinded safety data. At each meeting, the DSMB recommended continuation of the study without modification.

DSMB FINDING

DSMB Final Assessment (15 January 2026). The DSMB reviewed the final unblinded safety data and concluded that the overall benefit–risk profile of Brexiprant 300 mg remains favorable. No new safety signals were identified. The DSMB noted a modest, non-significant numerical imbalance in the rate of serious infections (1.8% Brexiprant vs. 0.9% placebo) and recommended routine post-marketing surveillance for this event category.

8.6 Clinical Laboratory Evaluations

No clinically meaningful differences in mean changes from baseline in hematology, clinical chemistry, or urinalysis parameters were observed between treatment groups. Grade ≥ 3 laboratory abnormalities were reported in 3.1% of Brexiprant-treated patients (most commonly ALT elevation: 2.0%; all transient and asymptomatic) and 2.2% of placebo-treated patients. One patient in the Brexiprant group met the protocol-defined criteria for potential Hy's Law (ALT $> 3\times$ ULN with concurrent total bilirubin $> 2\times$ ULN); the event resolved upon treatment discontinuation and was assessed as possibly related to study drug.

8.7 Vital Signs and Physical Findings

No clinically relevant changes in vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, body temperature) or physical examination findings were observed over the 52-week treatment period in either treatment group.

9 Discussion and Overall Conclusions

The BREX-301 study demonstrated that Brexiprant 300 mg administered orally once daily was significantly superior to placebo across all pre-specified primary and key secondary efficacy endpoints in adults with moderate-to-severe plaque psoriasis. The magnitude of the treatment effect was robust: the adjusted difference in PASI 75 response at Week 16 was 58.1% (95% CI: 52.4%, 63.8%; $p < 0.0001$), which is clinically meaningful and compares favorably with results from pivotal trials of currently approved biologic therapies in similar patient populations.

The onset of efficacy was rapid, with separation from placebo in PASI 75 response rates observed as early as Week 2 (22.4% Brexiprant vs. 2.7% placebo; nominal $p < 0.001$). Response rates continued to improve through Week 16 and were maintained through Week 52, with 75.2% of Brexiprant-treated patients achieving PASI 75 at Week 52. The proportions of patients achieving the more stringent thresholds of PASI 90 (48.8% at Week 16) and sPGA 0/1 (62.9% at Week 16) support a high degree of skin clearance with Brexiprant treatment. The clinically meaningful improvement in patient-reported DLQI scores further corroborates the benefit of Brexiprant from the patient perspective.

The safety profile of Brexiprant over 52 weeks was generally consistent with that observed in earlier-phase studies. The overall incidence of TEAEs, SAEs, and TEAEs leading to discontinuation was comparable between treatment groups. No new or unexpected safety signals were identified. The types of AEs observed were consistent with the target patient population and the known pharmacologic properties of brexiprant. Importantly, the oral route of administration represents a significant advantage over currently available biologic therapies, which require subcutaneous or intravenous administration.

Regulatory Implications. The results of BREX-301, together with the concurrently conducted BREX-302 study (a Phase III active-comparator trial vs. adalimumab), form the basis of a New Drug Application (NDA) planned for submission to the U.S. Food and Drug Administration and a Marketing Authorization Application (MAA) to the European Medicines Agency in Q3 2026.

In conclusion, Brexiprant 300 mg administered orally once daily demonstrated superior efficacy with a favorable safety profile in the treatment of moderate-to-severe plaque psoriasis over 52 weeks. If approved, brexiprant would represent the first oral targeted therapy for this indication, addressing a significant unmet need for patients who prefer or require an alternative to injectable biologic therapies.

10 Tables, Figures, and Listings Cross-Reference

Table 8 provides a cross-reference between the Statistical Analysis Plan (SAP, Version 2.0, dated 15 July 2025) and the relevant sections of this Clinical Study Report. The SAP was finalized and signed prior to database lock and treatment unblinding on 28 January 2026.

Table 8. Cross-Reference: Statistical Analysis Plan to Clinical Study Report

SAP §	SAP Description	CSR §
3.1	Study Objectives and Endpoints	**4**
4.1	Analysis Populations (FAS, PP, Safety)	**7.1, 6.1**
5.1	Sample Size Determination	**Synopsis**
6.1	Patient Disposition	**6.1**
6.2	Demographic and Baseline Characteristics	**7.1**
7.1	Primary Efficacy Analysis (PASI 75, Week 16)	**7.2**
7.2	Key Secondary Efficacy Analyses	**7.3**
7.3	Subgroup Analyses	**7.2**
7.4	Sensitivity Analyses for Missing Data	**7.2**
8.1	Extent of Exposure	**8.1**
8.2	Overall AE Summary	**8.2**
8.3	AEs by SOC and PT	**8.3**
8.4	Serious Adverse Events	**8.4**
8.5	Laboratory Evaluations	**8.5**
8.6	Vital Signs	**8.6**
9.1	Interim Analysis (Futility)	**5.5**
9.2	Multiplicity Adjustment	**5.5**

All tables, figures, and listings (TFLs) referenced in this report were produced using SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA) in accordance with CDISC standards (SDTM v1.8, ADaM v2.1). The complete set of TFLs is provided in Appendix 16.2.

11 Reference List

[1] ICH Harmonised Tripartite Guideline. Structure and Content of Clinical Study Reports (E3). Step 4 version, 30 November 1995.

[2] ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice (E6/R2). Step 4 version, 9 November 2016.

[3] World Medical Association. Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. *JAMA*. 2013;310(20):2191–2194.

[4] Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70(5):871–881.

[5] Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*. 2020;323(19):1945–1960.

[6] Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis — results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326–338.

[7] Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375(4):345–356.

[8] Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019;394(10201):831–839.

[9] Brexiprant Investigator's Brochure. Edition 7. Valkyra Bio Pharmaceuticals Corporation; 15 October 2025.

[10] Study BREX-201 Clinical Study Report. A Phase II, Randomized, Dose-Ranging Study of Brexiprant in Patients with Moderate-to-Severe Plaque Psoriasis. Valkyra Bio Pharmaceuticals Corporation; 05 March 2025.