25 June 2026
EMADOC-1700519818-3277186
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Dupixent

International non-proprietary name: dupilumab

Procedure No. EMA/VR/0000248778

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to PRAC/CHMP members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission deadline	5 February 2025	3 February 2025	☐
☐	Validation	21 February 2025	13 February 2025	☐
☐	Start date	22 February 2025	22 February 2025	☐
☐	CHMP Rapporteur AR	16 April 2025	16 April 2025	☐
☐	PRAC Rapporteur AR	25 April 2025	25 April 2025	☐
☐	PRAC comments	30 April 2025	n/a	☐
☐	Updated PRAC Rapporteur AR	2 May 2025	n/a	☐
☐	PRAC outcome	8 May 2025	8 May 2025	☐
☐	CHMP comments	12 May 2025	9 May 2025	☐
☐	Updated CHMP Rapporteur AR	15 May 2025	15 May 2025	☐
☐	Request for supplementary information	22 May 2025	22 May 2025	☐
☐	Submission of MAH responses	12 September 2025	10 September 2025	☐
☐	Re-start of procedure	15 September 2025	15 September 2025	☐
☐	CHMP Rapporteur Assessment Report	14 October 2025	15 October 2025	☐
☐	PRAC Rapporteur Assessment Report	17 October 2025	17 October 2025	☐
☐	PRAC comments	22 October 2025	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	23 October 2025	23 October 2025	☐
☐	PRAC outcome	30 October 2025	30 October 2025	☐
☐	CHMP members comments	3 November 2025	31 October 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	6 November 2025	6 November 2025	☐
☐	Request for supplementary information	13 November 2025	13 November 2025	☐
☐	Submission of MAH responses	23 January 2026	23 January 2026	☐
☐	Re-start of procedure	26 January 2026	26 January 2026	☐
☐	CHMP Rapporteur Assessment Report	2 March 2026	3 March 2026	☐
☐	CHMP members comments	16 March 2026	12 March 2026	☐
☐	Updated CHMP Rapporteur Assessment Report	19 March 2026	19 March 2026	☐
☒	Request for supplementary information	26 March 2026	26 March 2026	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Jan Mueller-Berghaus

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List of abbreviations

ABQOL	Autoimmune bullous disease quality of life
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIBD	Autoimmune bullous disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BP	Bullous pemphigoid
BPDAI	Bullous pemphigoid disease area index
BSA	Body surface area
CI	Confidence interval
C-R	Concentration-response
CSR	Clinical study report
Ctrough	Trough concentration
ECG	Electrocardiogram
FAS	Full analysis set
HLT	High level term
HR	Hazard ratio
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational medicinal product
IWRS	Interactive web response system
LS	Least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NAb	Neutralizing antibody
NRS	Numerical rating scale
OCS	Oral corticosteroids
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PRO	Patient-reported outcome
PT	Preferred term
PTT	Post-text Table
QoL	Quality of life
Q2W	Every 2 weeks
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation

SMQ	Standardized MedDRA query
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
Th2	T-helper type 2

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 03 February 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults with bullous pemphigoid (BP) for DUPIXENT, based on final results from study R668-BP-1902 (LIBERTY-BP ADEPT); this is a phase 2/3, multicenter, randomized, double blind, placebo-controlled, parallel group study to assess the efficacy and safety of dupilumab in adult patients with bullous pemphigoid; As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated accordingly. The Package Leaflet is also updated in accordance. Version 12.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0304//2020) on the granting of a product-specific waiver for the treatment of Bullous Pemphigoid.

Information relating to orphan market exclusivity

N/A

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14 November 2019. The Scientific Advice pertained to the suitability of the proposed phase 3 study design to evaluate the efficacy and safety of dupilumab in BP as well as the overall sufficiency of the current clinical development plan to support registration in the proposed indication.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

BP is a rare, autoimmune subepidermal blistering disease primarily affecting the elderly. The disease is characterized by large, tense, serous, or hemorrhagic bullae arising on erythematous, urticarial, or eczematous skin together with the presence of itch. Mucosal lesions that involve oral, esophageal or genital mucosa can also develop but are less common. The severity of itch, physical discomfort and pain associated with cutaneous lesions significantly disturbs the quality of life in affected patients. The disease presents with a chronic relapsing course that may last from months to several years.

State the claimed the therapeutic indication

The initially proposed indication is as follows:

Dupixent is indicated for the treatment of adults with bullous pemphigoid.

Epidemiology

The incidence of BP has increased over the past 2 decades, in part, likely due to increased life expectancy and better diagnostic methods. A recent systematic review and meta-analysis estimated the global incidence of BP at 41.9 cases/million/year, and by continent at 47 cases/million/year in North America, 41.9 cases/million/year in Europe, 7.2 cases/million/year in Asia, and 3 cases/million/year in Africa (Lu, 2022). The mean age of onset is between 66 to 83 years across different populations worldwide.

Given its predilection for the elderly and its frequent recurrences, BP is associated with high disease burden, morbidity, and mortality. The standardized mortality rate in patients with BP has been estimated in a meta-analysis at over 3-fold higher than age- and sex-matched controls often due to complications related to the disease, such as secondary infections or adverse effects of the medications required for disease control (Kridin, 2018c). The reported mortality rate during the first year in the bullous phase of disease varies between 10% and 40%. Moreover, BP has been associated with multiple infectious, cardiovascular, and neuropsychiatric comorbidities, resulting in a higher healthcare burden, hospitalization rate, and mortality rate for those with BP than without BP.

Aetiology and pathogenesis

BP is characterized by the presence of circulating autoantibodies against BP180 (BPAG2 or type XVII collagen) and BP230 (BPAG1e – epithelial isoform), structural proteins of the hemidesmosomes, at the epidermal-dermal junction and responsible for the adhesion between the epidermis and dermis. NC16A, a non-collagenous ectodomain of the BP180, is the primary target of the autoantibodies in patients with BP, predominantly IgG4 and IgE. Detection of anti-BP180 autoantibodies is one of the diagnostic criteria for BP. Once anti-NC16A autoantibodies bind to BP180, several pathways are

activated, including complement activation and deposition, neutrophilic chemotaxis with release of proteases and elastases and resulting degradation of the basement membrane. Both IgG and IgE autoantibodies are involved in the induction of subepidermal blisters and IgE autoantibodies are presumed to be the cause of the pruritic and erythematous features of BP. Eosinophils are the most common cell type observed in histological analysis of the BP skin lesions along with elevated blood eosinophils. Elevated serum and blister-fluid levels of soluble inflammatory Th2 cells response mediators (eg, IL-4, IL-13, TARC/CCL17, PARC/CCL18) have been described in large cohorts of patients with BP. The levels of TARC/CCL17 and PARC/CCL18 correlate with disease severity.

Clinical presentation / Diagnosis

Diagnosis of BP is based on characteristic clinical features (large, tense, serous, or hemorrhagic bullae arising on erythematous, urticarial, or eczematous skin), positive direct immunofluorescence with linear deposits of IgG and/or complement C3 along the dermal–epidermal junction (essential for diagnosis) and supported by detection of IgG autoantibodies against BP180 and/or BP230 in serum by enzyme-linked immunosorbent assay and/or indirect immunofluorescence.

Management

The latest guidelines for managing BP recommends treating BP based on the severity of BP and the patient's comorbidities, typically starting initially with topical or oral corticosteroids (OCS) with the aim to achieve disease control (Borradori, 2022). Disease control is defined as the point at which new lesions or pruritic symptoms cease to form and established lesions begin to heal (Murrell, 2012). Potent or super potent topical corticosteroids can be applied on affected skin regions while long-term application is not recommended for sensitive skin areas or for large body surface area, which may result in substantial systemic absorption. High or medium dose OCS therapy can be initiated to rapidly establish control of disease.

The prolonged use of high dose systemic or topical corticosteroid therapy is not recommended given the elderly patient population and the associated side effects. Once disease control has been achieved corticosteroids should be tapered expeditiously to the minimal effective dose that can control the disease. BP relapses are frequent especially when corticosteroids are being tapered or while being weaned off corticosteroids completely. The relapse rate of BP ranges from 27.87% to 53% after disease remission, while the majority of relapses occur early (within 6 months) during remission.

Doxycycline or dapsone have also been utilized in conjunction with corticosteroids as steroid sparing agents. For recalcitrant BP responding poorly to OCS, or relapsing disease associated with OCS taper, broad systemic immunosuppressive agents (eg, mycophenolate mofetil, methotrexate, cyclophosphamide) or biologics (eg, rituximab, omalizumab) are sometimes added.

Unmet medical need

Patients with BP have a high disease burden. The severity of itch, physical discomfort and pain significantly disturbs the quality of life in affected patients. The disease has an increased morbidity, and mortality due to associated infectious, cardiovascular, and neuropsychiatric comorbidities.

The current standard-of-care therapies (that are primarily based on oral or topical corticosteroids) are associated with significant side effects which limit their use in the vulnerable elderly BP population with BP. Disease relapses frequently occur when corticosteroids are tapered. Given that patients often rely on corticosteroid use and that much of the excess morbidity and mortality in this disease is related to

the effects of systemic corticosteroids and immunosuppressants in the first year after onset of bullous disease, alternatives are urgently needed.

An unmet medical need exists for new treatment options that target the underlying inflammatory process to control disease activity, reduce skin and pruritic symptoms, maintain long-term remission while minimizing the need for additional corticosteroid or other immunosuppressive treatments (Borradori 2022, Kridin 2018, Lu 2022, Murrell 2012)..

2.1.2. About the product

Dupixent (dupilumab) is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. By blocking signaling of both IL-4 and IL-13 which are key cytokines involved in type 2 inflammation, dupilumab broadly suppresses type 2 inflammation.

Dupilumab is approved in the EU for the following indications:

- Atopic dermatitis

Adults and adolescents

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age

Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy.

- Asthma

Adults and adolescents

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who are inadequately controlled with high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age

Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide who are inadequately controlled with medium to high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

- Chronic rhinosinusitis with nasal polyposis (CRSwNP)

Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

- Prurigo Nodularis (PN)

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

- Eosinophilic esophagitis (EoE)

Dupixent is indicated for the treatment of eosinophilic esophagitis in adults, adolescents and children aged 1 year and older, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

- Chronic obstructive pulmonary disease (COPD)

Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

- Chronic Spontaneous Urticaria (CSU)

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naive to anti-IgE therapy for CSU.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant received Scientific Advice by CHMP on 14 November 2019. The scientific advice pertained the suitability of the proposed phase 3 study design to evaluate the efficacy and safety of dupilumab in BP as well as the overall sufficiency of the current clinical development plan to support registration in the proposed indication.

2.1.4. General comments on compliance with GCP

A study site monitoring plan including monitoring visits and source data verification visits was in place. Given the pandemic situation during the study conduct remote monitoring visits were implemented. The monitoring plan was provided during the procedure upon EMA request. From the information provided, Source Data Verification was performed continuously with only one-time SDV performed. no final bulk verification for the most critical source data was implemented.

Risk-based audits at three clinical sites (France, Australia and USA) were conducted. The audits revealed deficiencies in the area of Source Documentation management on the sample of data reviewed. As claimed by the MAH, CAPA plans were provided to address the findings.

Of note, following clinical study site inspections by the US FDA, inconsistencies between source documents and data entered by the study sites into the electronic data capture (EDC) system were observed at the 2 inspected sitesin France and Australia, the same sites that had been audited by the sponsor previously. The inspection findings led to corrections of the results for the primary endpoints of the study leading to a non-significant result.

As data discrepancies in the source data already existed at the time of the audit it is unclear why the audit was not able to identify the issues in source data. This observations sheds uncertainties on how well the study was actually supervised and whether other data deficiencies may exist in other non-inspected sites.

3. Quality/Non-clinical aspects

The applicant provided in section 3.2.R the Justification for no need of Notified Body Opinion - MDR Article 117. The applicant sufficiently outlined that there are no changes to the design or intended purpose of the device 300mg PFS with safety device and 300mg prefilled pen presentations, nor is there a new medical device being introduced. The justification for not providing the notified body opinion is acceptable.

The applicant sufficiently outlined that the characteristics of the intended user and use environment for the new BP indication is supported by existing usability data for the authorized presentations. Therefore, it can be agreed that an additional usability study is not required.

No new non-clinical data have been submitted in this application, which is considered acceptable.

4. Clinical aspects

4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

Also refer to Section above (General comments on compliance with GCP).

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical development program to assess dupilumab for use in BP consists of the single pivotal study R668-BP-1902.

Table 1. Overview of Study R668-BP-1902

Study ID / Design / Control Type / Cutoff Date / Study Status	Study Population	Treatment / Dose Regimen / Route of Administration	Number of Participants Treated	Duration of Treatment	Primary Efficacy Endpoint
R668-BP-1902 Randomized (1:1), double-blind, placebo-controlled, parallel group 18 Feb 2025 Completed	Adults with moderate-to-severe BP as determined by documented diagnosis of BP based on histopathology, immunopathology, and serology; a BPDAI activity score ≥24; and a peak NRS for maximum itch intensity ≥4 at baseline; and a minimum Karnofsky Performance Status Scale score of 50% at the screening visit.	**Dupilumab** administered SC; loading dose of 600 mg, followed by 300 mg Q2W **Placebo** administered SC; loading dose, followed by Q2W	**Enrolled**: 106 **Dupilumab**: 53 **Placebo**: 53	52-week treatment duration, with 12-week follow-up	Proportion of participants achieving sustained remission at week 36

Study ID / Design / Control Type / Cutoff Date / Study Status	Study Population	Treatment / Dose Regimen / Route of Administration	Number of Participants Treated	Duration of Treatment	Primary Efficacy Endpoint
		All participants received background treatment OCS (prednisone or prednisolone). Tapering of OCS was to begin when there had been 2 weeks of sustained control of disease activity.			

4.2. Pharmacokinetics in adult patients with BP

Bioanalytical methods

Bioanalytical methods for investigation of dupilumab serum concentrations as well as immunogenicity (ADA and NAb) are the same as previously assessed in the original marketing application. Methods were validated according to EMA guideline.

Functional dupilumab concentrations, immunogenicity, and PD data for dupilumab in the treatment of participants with moderate-to-severe BP have been collected in one phase 2/3 clinical study in adults (Study R668 BP 1902).

Pharmacokinetic data analysis

Samples for the analysis of functional dupilumab concentrations in serum were collected in **Study R668-BP-1902** according to a protocol-specified **sparse collection schedule**, which included a baseline sample (ie, collected prior to treatment initiation) and Ctrough samples collected at week 4, week 16, week 36, week 52/ EOT, and week 64/ EOS.

Concentrations of dupilumab were presented using descriptive statistics by nominal sampling time and treatment group. In these descriptive assessments, concentrations below the LLOQ were set to 0 (except for geometric mean, for which LLOQ/2 was imputed). Plots of mean concentrations were presented by nominal time. In linear scaled plots, concentrations below the LLOQ were set to 0, and in log scaled plots, concentrations that were BLQ were imputed as LLOQ/2.

SAS version 9.4 and R version 4.3.1 were used for statistical analysis to generate analysis datasets, tables, figures, or listings.

The **population PK analysis of dupilumab** in participants with BP was based on an **external validation approach** using a recent reference model developed to describe the pharmacokinetics of dupilumab in healthy subjects and participants with EoE (Module 5.3.3.5 R668-PK-23108-SR-01V1 of the Pediatric EoE marketing application). This model was selected as the reference model because it included a wide range of participant body weights from adults through children as young as 1 year of age to characterize the effects of allometry on PK parameters. The reference model structure consisted of a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination, and first-order SC absorption with a transit delay. The reference model also included covariate effects for body weight on clearances and volumes, albumin on clearance, and patient population effects on VC, CL, Vmax, and residual error to adjust these parameters between healthy volunteer and patient

populations and study designs. Nonlinear mixed effects modeling methodology was implemented in this analysis.

The adequacy of the reference model to characterize observed concentrations of dupilumab in participants with BP was assessed via an external prediction-corrected visual predictive check (pcVPC). Parameter estimates were fixed to estimates from the reference model and used to generate datasets (N = 1000) which replicated the design, dose regimen, sample size, and covariate distribution for participants from Study R668-BP-1902. Appropriate statistical intervals (eg, median, 5th and 95th percentiles) of dupilumab concentrations were computed at nominal PK time points in the observed dataset and each of the simulated datasets. The observed and simulated summary metrics were plotted to provide a visual assessment of the predictive performance of the previous PK model in adult participants with BP.

The reference model was then used to generate post-hoc estimates of pharmacokinetic parameters for participants in Study R668-BP-1902.

To characterize exposure of dupilumab at steady-state, population simulations were performed by drawing 1000 random participants, with replacement from the BP dataset. The resampled participant's baseline body weight and baseline albumin were adjusted with random noise (CV=10%) and used to simulate 52 weeks of treatment with the study regimen of dupilumab 300 mg Q2W, including a 600 mg loading dose on day 1.

Test and reference products, doses and mode of administration

The selected SC dosing regimen in participants with BP was **dupilumab 300 mg Q2W after a loading dose of 600 mg**. The 300 mg Q2W regimen has already demonstrated a favorable risk-benefit profile and is approved for adults with AD, asthma, CRSwNP, PN, and COPD.

For AD, a loading dose is administered to more rapidly achieve effective dupilumab concentrations, thereby, allowing a rapid onset of response as demonstrated by improvement in pruritus, a hallmark of AD, as early as 2 weeks after the start of treatment. Pruritus is also a core symptom of BP; hence, a loading dose was included for evaluation of dupilumab in participants with BP in Study R668-BP-1902.

A **dupilumab-matching placebo** was used as comparator.

All participants, regardless of treatment assignment, received a **standard background regimen of OCS** (prednisone or prednisolone) starting on day 1/baseline visit to obtain control of disease. Participants underwent a protocol-defined OCS tapering regimen with the objective to taper off OCS completely no later than week 16, as long as they maintained control of disease activity.

PK objectives end endpoints

Study R668-BP-1902

Secondary PK objective: To characterize the trough concentrations of functional dupilumab over time following administration of dupilumab in participants with BP

Secondary PK endpoint: Concentrations of functional dupilumab in serum at each scheduled sampling time point from baseline to the end of study (up to week 64)

The primary objectives of the PopPK analysis were to:

- Assess the PK of dupilumab in adult patients with BP using an external validation approach with a PopPK model developed for EoE in adults and pediatric patients
- Update the PopPK model developed for dupilumab in adults and pediatric patients with EoE with the addition of PK data in adult patients with BP, if necessary

- Generate individual subject PK parameters and exposure predictions across all, Japanese/Non-Japanese and Asian/non-Asian populations

Analysis Sets and Study Subjects

The PKAS includes all randomized participants who received any study drug (active, SAF) and had at least 1 non-missing result following the first dose of any study drug. Analysis is based on the treatment received.

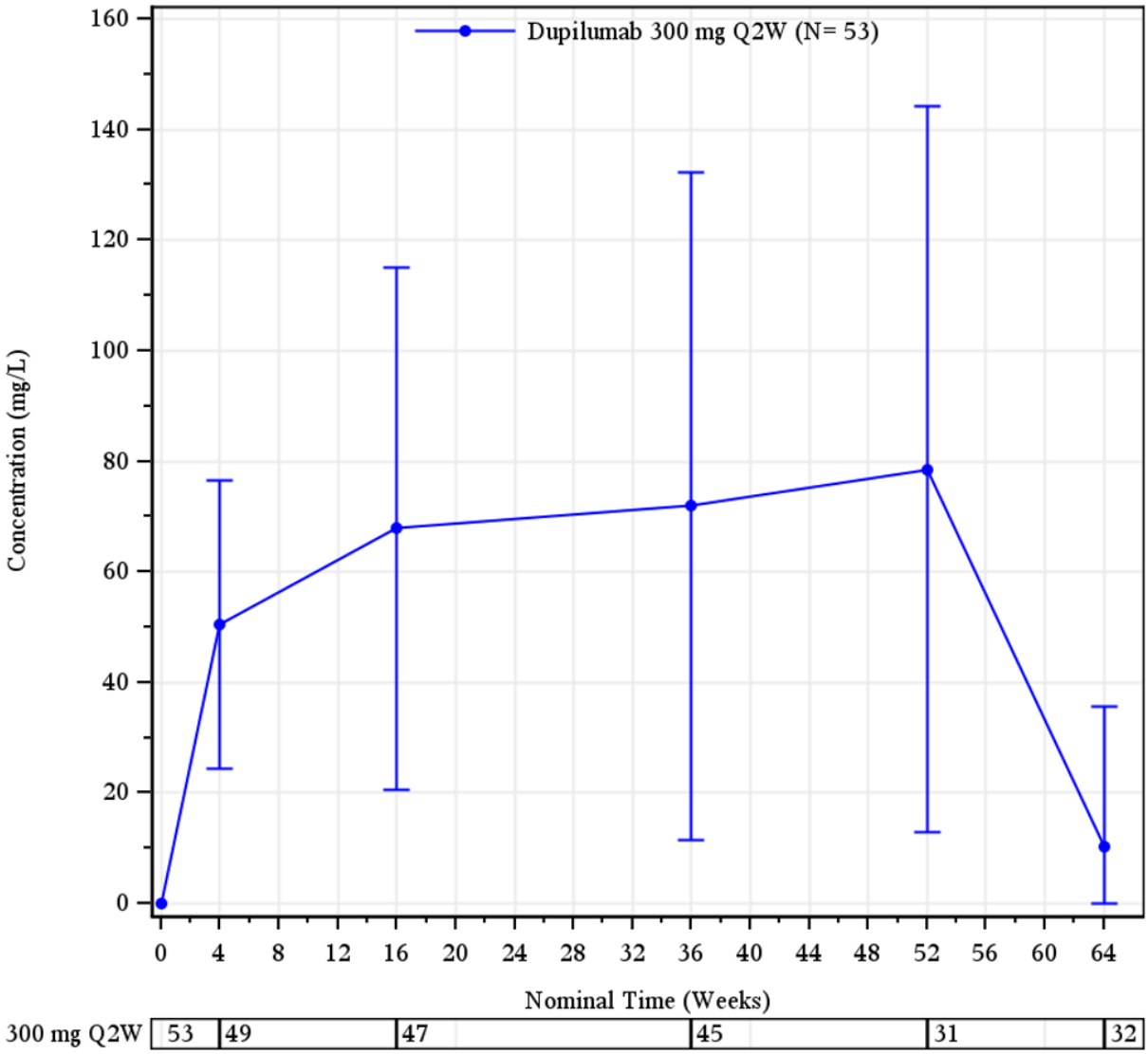
All Subjects included in the Safety Analysis Set and treated with Dupilumab were included in the PKAS (N=53).

The dataset for the population PK analysis of dupilumab included a total of 53 unique participants with BP and 225 PK samples, with 198 (88%) quantifiable samples and 27 (12%) post-dose samples that were BLQ.

PK outcomes Study R668-BP-1902

The functional **dupilumab Ctrough in serum** was at or near steady-state by week 16 in participants with BP treated with dupilumab 300 mg Q2W. The mean (SD) dupilumab Ctrough was 67.9 (47.2) mg/L at week 16, 71.9 (60.3) mg/L at week 36, and 78.5 (65.6) mg/L at week 52 up to data cutoff.

Figure 1. Mean (±SD) Concentrations of Functional Dupilumab in Serum by Time and Treatment Group (R668-BP-1902 PKAS)



Note: Concentrations below the LLOQ are set to 0. The table under the figure presents the number contributing to the statistics for the corresponding visits and treatment group.

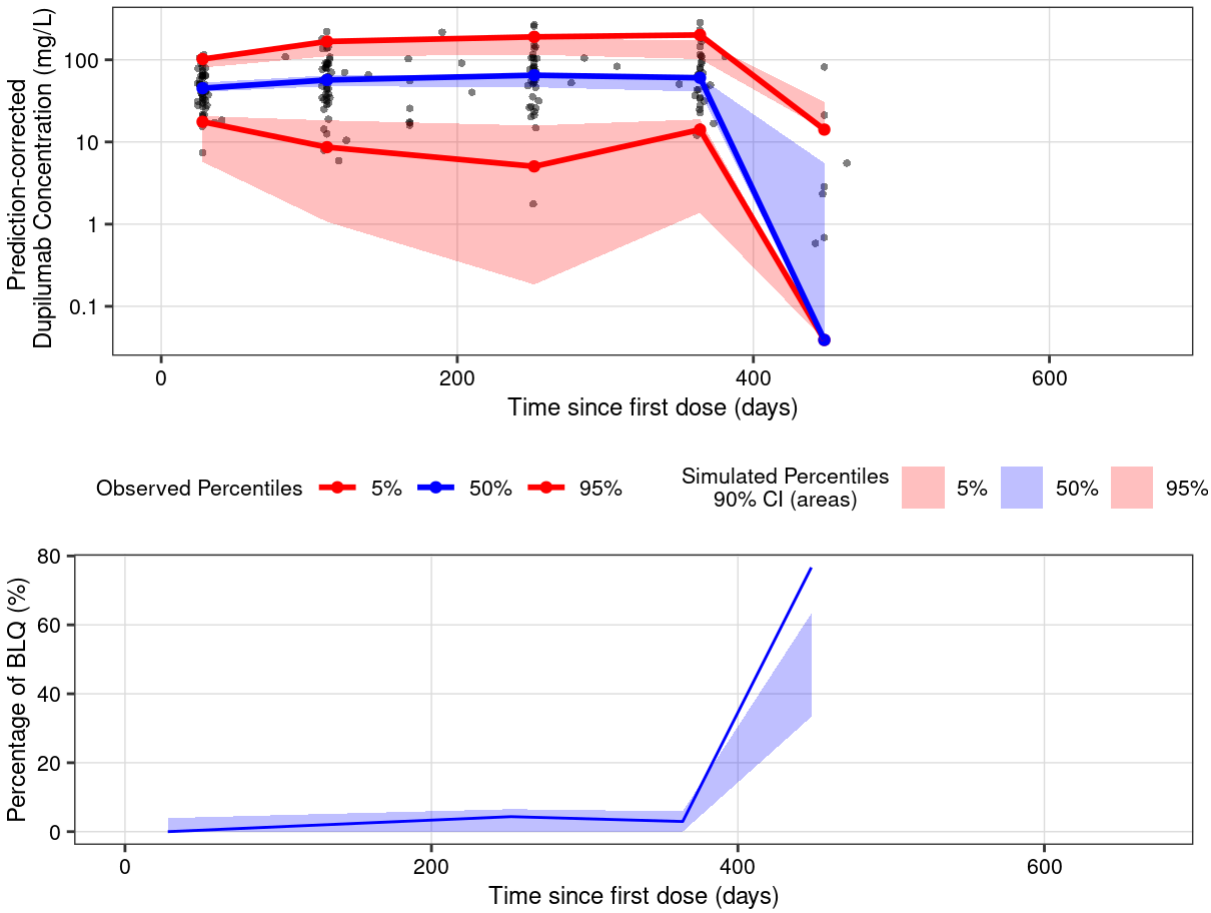
Note: Week 52 and week 64 PK data were included in the analysis if samples were available at the time of data cutoff.

Abbreviations: LLOQ=lower limit of quantitation; N=number of participants in each treatment group; PK=pharmacokinetic; PKAS=pharmacokinetic analysis set; Q2W=every 2 weeks; SD=standard deviation.

Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis Appendix 16.1.14 PTF 7.2.4.01

Population PK external validation

Figure 2. External Prediction-Corrected Visual Predictive Check - Reference Dupilumab PK Model with BP Participant Data



The population median is provided by the blue line, and the 5th and 95th percentiles are indicated by the red lines. The shaded bands represent the 90% confidence intervals of the median and percentiles generated from the model. The observed data is plotted using time since first dose and represented by the black points. Data were grouped by bins at 70, 240, 308, and 406 days. The LLOQ of dupilumab was 0.078 mg/L.
Abbreviations: BLQ = Below the level of quantification; CI = Confidence Interval; LLOQ = lower limit of quantification.
Source: Module 5.3.3.5 R668-PM-24222-SR-01V1 Figure 1.

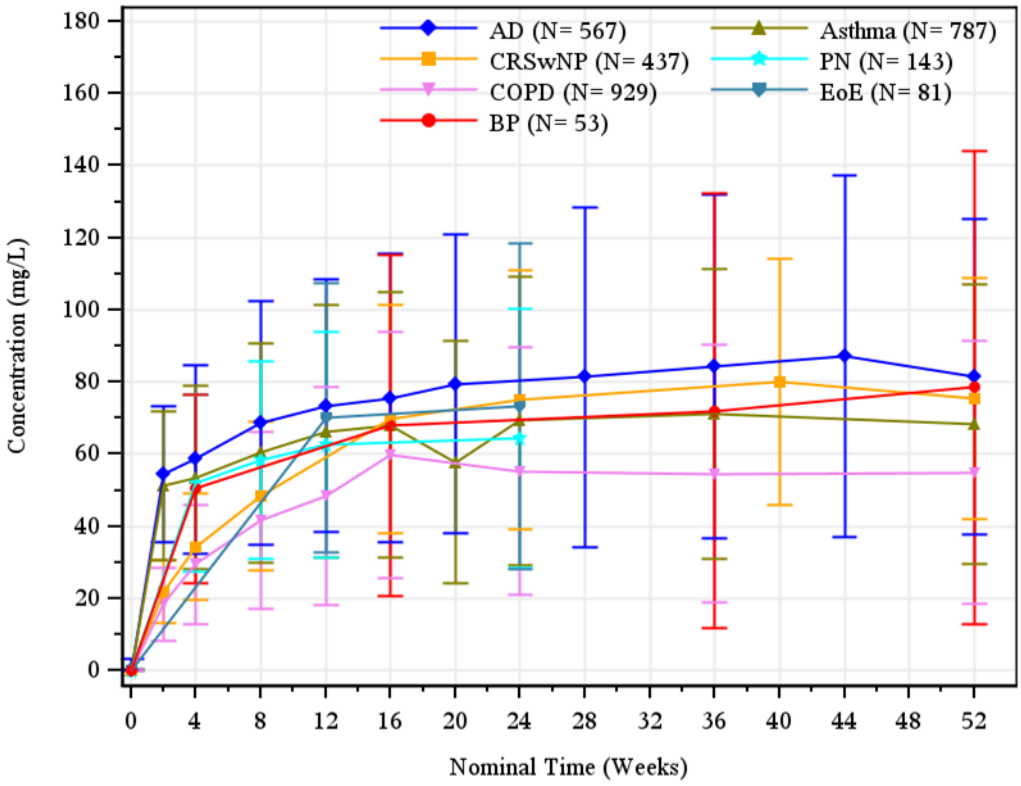
With an adequate pcVPC and unbiased empirical bayes estimates, the previously developed reference popPK model was deemed suitable for use in determining post-hoc exposure and predicting concentrations in the BP population.

PK comparison across indications

Mean Ctrough of functional dupilumab over time in participants with BP from Study R668-BP-1902 were compared to participants with AD, asthma, CRSwNP, PN, COPD, and EoE who received dupilumab 300 mg Q2W for up to 52 weeks. The analysis set for the concentrations of functional dupilumab includes adults in each study where each respective disease was evaluated, as well as adolescents for studies that included both adults and adolescents receiving 300 mg Q2W.

The week 36 mean (SD) Ctrough of dupilumab at steady-state for adults with BP was reported to be 71.9 (60.3) mg/L (n=45), within the range observed in other disease populations who received dupilumab 300 mg Q2W.

Figure 3. Concentrations of Functional Dupilumab in Serum by Nominal Time (Weeks) and Indication in Participants with BP, AD, Asthma, CRSwNP, PN, COPD, and EoE Receiving Dupilumab 300 mg Q2W (PKAS)



Note:

Concentrations below the LLOQ (0.078 mg/L) are set to 0. Participants shown during treatment with dupilumab 300 mg Q2W for 0 to 52 weeks and pooled by indication.

Studies by indication include AD (R668-AD-1334, R668-AD-1416, R668-AD-1224), Asthma (EFC13579, DRI12544), CRSwNP (EFC14280, EFC14146), PN (EFC16459, EFC16460), COPD (EFC15804, EFC15805), EoE (R668-EE-1774 Part B), and BP (R668-BP-1902).

Dupilumab was administered with a 600 mg loading dose on Day 1 in BP, AD, Asthma, and PN studies. No loading dose was used in CRSwNP, COPD, and EoE studies.

Study EFC13579 included adults and adolescent participants with asthma.

Study R668-EE-1774 Part B included adults and adolescent participants with EoE.

Abbreviations: AD=Atopic Dermatitis; BP=Bullous Pemphigoid; COPD=Chronic Obstructive Pulmonary Disease; CRSwNP=Chronic Rhinosinusitis with Nasal Polyps; EoE=Eosinophilic Esophagitis; LLOQ=Lower limit of quantitation; N=Number of participants in each indication; PKAS= PK analysis set; PN=Prurigo Nodularis; Q2W=Every 2 weeks.

Source: R668-SCP-BP_20241120 Figure 1.2.01.

Absorption, Distribution, and Elimination

The parameters of dupilumab disposition in participants with BP are consistent with those reported for dupilumab in the AD, asthma, CRSwNP, PN, COPD, and EoE populations based on observed data as well as population PK analysis utilizing the reference population PK model. Dupilumab was absorbed with a bioavailability of 66%. The typical Vss in the BP population was 5.01 L, based on a reference body weight of 70 kg for a typical participant.

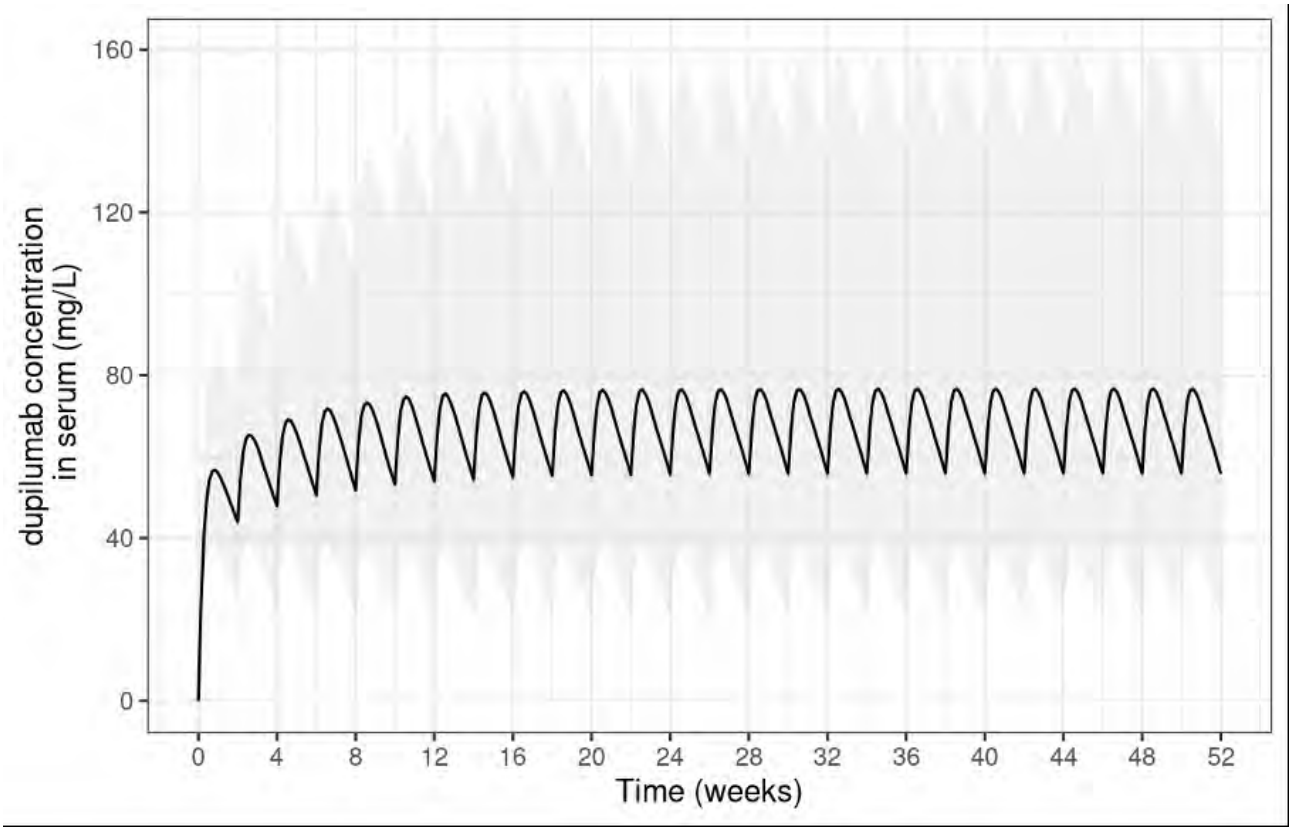
Dose proportionality and time dependencies

Dupilumab, like many other monoclonal antibody therapeutics, is characterized by parallel linear and non-linear target mediated kinetics. This non-linear PK profile is typically observed at drug concentrations below what is required to saturate the target-mediated pathway, resulting in a greater than dose-proportional increase in exposure. As drug concentrations increase to levels greater than those required to saturate the target-mediated pathway, the PK profile reverts to a linear and dose-proportional profile.

Observed concentrations of functional dupilumab in Study R668-BP-1902 suggest dupilumab was at, or near, steady-state by 16 weeks of starting dupilumab.

The predicted concentration-time profiles are illustrated in the Figure 4 below. Virtual participants (N=1000) were assigned the protocol-defined dupilumab dose of 300 mg Q2W and simulated for 52 weeks with daily PK sampling.

Figure 4. Exposure Predictions (IPRED) Over Time for Patients with BP (N = 1000)



BP = Bullous pemphigoid; IPRED = Individual prediction; N = Number of subjects
The population median is provided by the line, and the 5th and 95th percentiles are indicated by shaded region.

The overall mean (SD) and median (5th, 95th percentile) values for steady-state exposures were as follows: for AUCtau, 1080 (552) mg*day/L and 953 [433, 2080] mg*day/L; for Cmax, 85.5 (40.7) mg/L and 76.7 [37.6, 159] mg/L; and for Ctrough, 64.6 (37.4) mg/L and 55.9 [21, 134] mg/L.

Special populations

Body Weight

Body weight is the primary covariate affecting the PK of dupilumab in adult participants with BP (39.8 to 150 kg), consistent with previous findings in other disease populations and age groups. Increasing body weight is associated with decreasing concentrations of dupilumab at a fixed dose.

Table 2. Exposure Predictions by Weight Categories (Quartiles) for Dupilumab for BP Patients

Covariate	Category		AUC_{tau} (mg*day/L)	C_{max} (mg/L)	C_{trough} (mg/L)
Overall		Mean (SD)	1080 (552)	85.5 (40.7)	64.6 (37.4)
		Median [5th, 95th]	953 [433, 2080]	76.7 [37.6, 159]	55.9 [21, 134]
Baseline Weight (kg)	[31.2,60.9]	Mean (SD)	1590 (650)	124 (47)	97.3 (45.3)
		Median [5th, 95th]	1470 [797, 2820]	116 [66.4, 213]	88.4 [43.2, 182]
	(60.9,73.9]	Mean (SD)	1140 (403)	90.5 (29)	68.6 (28.4)
		Median [5th, 95th]	1080 [618, 2000]	85.8 [51.9, 151]	64.5 [32.9, 129]
	(73.9,89]	Mean (SD)	937 (345)	74.5 (24.9)	55.7 (24.1)
		Median [5th, 95th]	884 [445, 1530]	70.8 [39.1, 117]	52.1 [22, 96.9]
	(89,173]	Mean (SD)	651 (223)	52.9 (16.3)	36.9 (15.3)
		Median [5th, 95th]	624 [330, 1080]	51.2 [29.4, 84.3]	34.8 [15.3, 66.4]

AUCtau = Area under the concentration-time curve between 34 to 36 weeks; BP = Bullous pemphigoid; Cmax = Maximum concentration at week 34-36; Ctrough = Trough concentration at week 36; N for each covariate quartile = 250 subjects; Overall N = 1000 subjects; SD = Standard deviation

Age

In the development of the reference model, the population PK analysis demonstrated that after accounting for body weight, age was not a significant covariate on the PK of dupilumab in the final model.

Exposure metrics (mean, SD) by age groups (age 18 < 65, 65 < 75, and ≥ 75 years) are given in the Table 3 below.

Table 3. Summary Statistics (Mean [95% Confidence Interval]) of Individual Post-Hoc PK Parameters

Age (year)	N (Mean Weight (kg))	AUC_{tau} (mg*day/L)	C_{max} (mg/L)	C_{trough} (mg/L)
Overall	53 (76.6)	1140 (605)	89.5 (44.3)	68.8 (41.4)
≥18 - <65	13 (84.4)	1240 (706)	96.1 (51.8)	76.3 (48.2)
≥65 - <75	18 (72.6)	1030 (486)	81.9 (35.7)	60.9 (32.8)
≥75	22 (75.2)	1170 (644)	91.7 (47.1)	70.9 (44.2)

CL = Clearance; NA = Not applicable due to N = 1; N = Number of subjects; PK = Pharmacokinetic; Vc = Central volume of distribution

Table 4. Exposure Predictions by Age Group for Dupilumab for BP Patients

Age (year)	N (Mean Weight (kg))		AUC_{tau} (mg*day/L)	C_{max} (mg/L)	C_{trough} (mg/L)
Overall	1000 (76.2)	Mean (SD)	1080 (552)	85.5 (40.7)	64.6 (37.4)
		Median [5th, 95th]	953 [433, 2080]	76.7 [37.6, 159]	55.9 [21, 134]
≥18 - <65	234 (78.4)	Mean (SD)	1140 (557)	89.7 (41.1)	68.9 (37.5)
		Median [5th, 95th]	1070 [443, 2050]	85.4 [37.7, 157]	63.8 [22.8, 131]
≥65 - <75	341 (75.3)	Mean (SD)	1070 (558)	84.4 (40.8)	63.6 (38.2)
		Median [5th, 95th]	942 [438, 2030]	75.8 [38.4, 156]	54.3 [20.6, 132]
≥75	425 (75.8)	Mean (SD)	1060 (544)	84 (40.3)	63.1 (36.6)
		Median [5th, 95th]	932 [422, 2110]	75 [37.5, 161]	53.3 [20.8, 135]

AUCtau = Area under the concentration-time curve between 34 to 36 weeks; BP = Bullous pemphigoid; Cmax = Maximum concentration at week 34-36; Ctrough = Trough concentration at week 36; N = Number of subjects; SD = Standard deviation.

4.3. Pharmacodynamics

Mechanism of action

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the type I receptor and both IL-4 and IL-13 signaling through the type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, and IgE, therefore, broadly suppressing type 2 inflammation.

Primary and secondary pharmacology

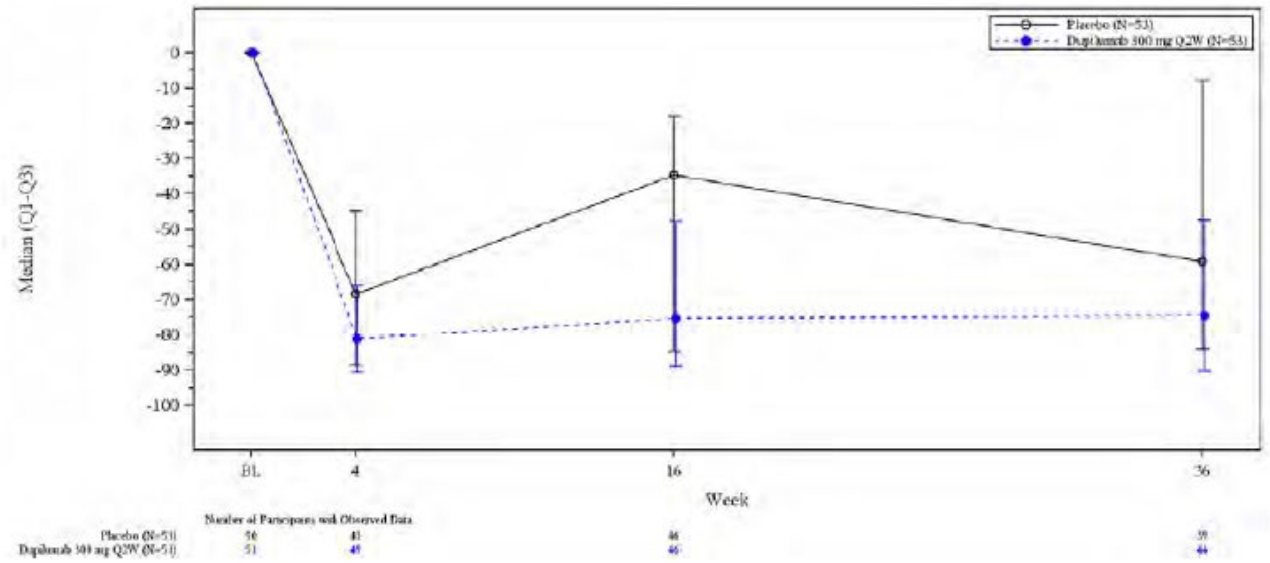
During the treatment period in Study R668-BP-1902, **TARC** and **IgE** were measured in serum at baseline and at week 4, week 16, week 36, and week 52/ EOT.

IL-4 and IL-13 induce the mRNA expression of TARC, a type 2 chemokine that attracts inflammatory cells to tissue. Thus in serum, TARC is a PD marker for inhibition of IL-4Rα signaling by dupilumab. Dupilumab also blocks B cell isotype class switching to form new IgE, leading to a decrease in systemic total IgE concentrations. TARC and total IgE concentrations in serum are known biomarkers of the type 2 inflammatory pathway.

Pharmacodynamic endpoints were assessed using the safety analysis set (SAF), which included all randomized participants in Study R668-BP-1902 who had received any study drug.

The median baseline concentration of TARC in serum was 1420.00 pg/mL in the dupilumab 300 mg Q2W group and 1175.00 pg/mL in the placebo group. At week 36, the median change from baseline in TARC was −723.00 pg/mL in the dupilumab 300 mg Q2W group and −325.00 pg/mL in the placebo group.

Figure 5. Median (Q1-Q3) Percent Change from Baseline in Concentration of TARC (CCL17) in Serum up to Week 36, All Observed Values (FAS)

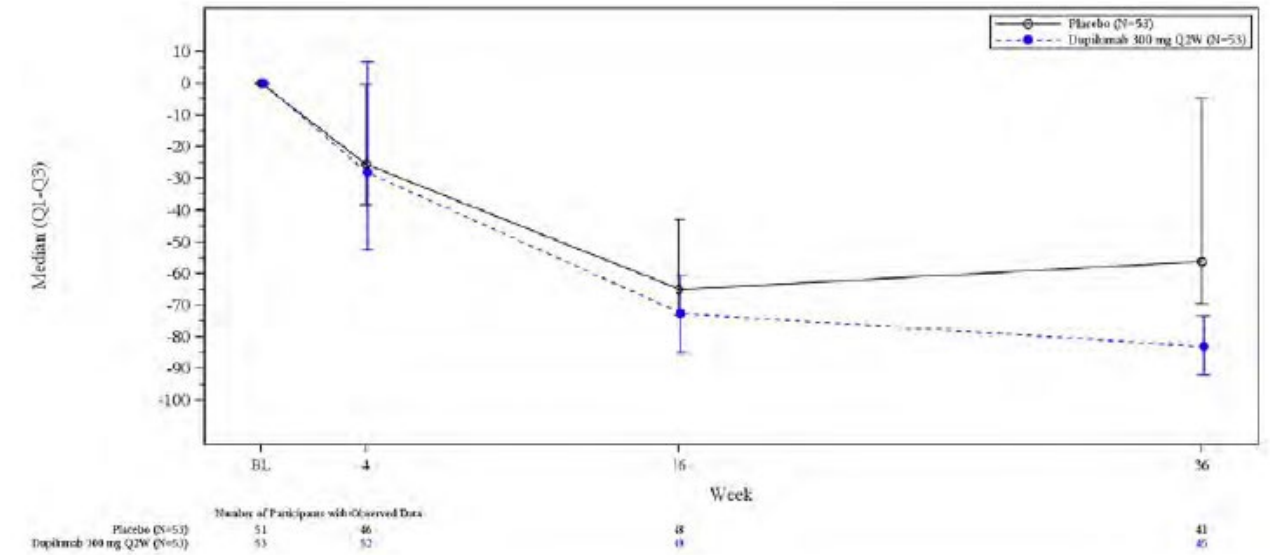


Note: All participants in both treatment groups were started on OCS at randomization with taper beginning by week 6 with the objective to taper off by week 16.

Abbreviations: BL=baseline; CCL17=chemokine (C-C motif) ligand 17; FAS=full analysis set; N=number of participants; OCS=oral corticosteroids; Q1=first quartile; Q2W=every 2 weeks; Q3=third quartile; TARC=thymus and activation-regulated chemokine.

Median baseline concentration of total IgE in serum was 424.00 kU/L in the dupilumab 300 mg Q2W group and 580.00 kU/L in the placebo group. At week 36, the median change from baseline in total IgE was −377.00 kU/L in the dupilumab 300 mg Q2W group and −207.50 kU/L in the placebo group.

Figure 6. Median (Q1-Q3) Percent Change from Baseline in Concentrations of Total IgE in Serum up to Week 36, All Observed Values (FAS)



Note: All participants in both treatment groups were started on OCS at randomization with taper beginning by week 6 with the objective to taper off by week 16.

Abbreviations: BL=baseline; FAS=full analysis set; IgE=immunoglobulin E; N=number of participants; OCS=oral

corticosteroids; Q1=first quartile; Q2W=every 2 weeks; Q3=third quartile.
Source: PTF 14.2.4.3

4.4. PK/PD modelling

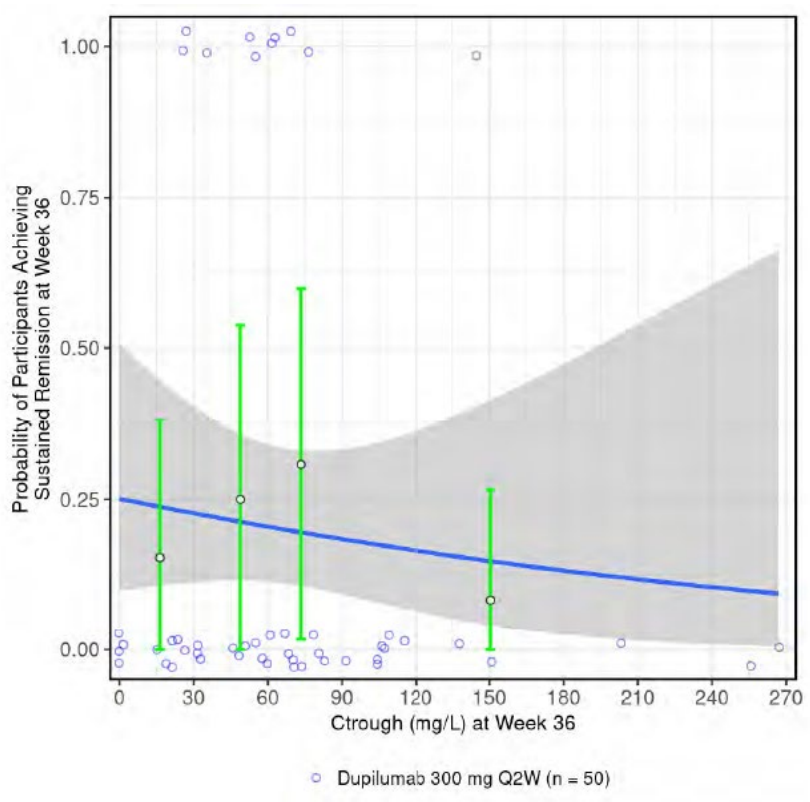
Analysis of Concentration-Response Relationships

Concentration-Response analyses were conducted to evaluate the relationship between concentrations of functional dupilumab and the clinical response variables.

The Concentration-Response-Analysis-Set (CRAS) consists of participants in the PKAS with an observed sustained remission status at week 36, or 1 non-missing baseline and at least 1 post dose BPDAI activity score value, as applicable for each C-R assessment.

Clinical response variables for **efficacy** were based on the primary endpoint, which measured the proportion of participants achieving sustained remission of BP at week 36, and a key secondary endpoint, which measured the percent change from baseline in BPDAI activity score (ie, BP disease activity) to week 36.

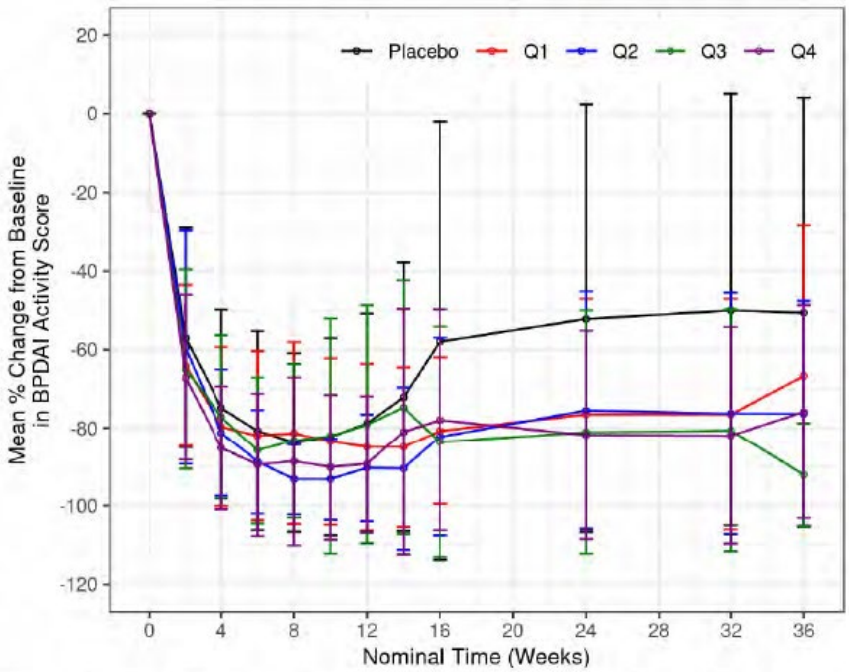
Figure 7. Logistic Regression Relating Probability of Participants Achieving Sustained Remission at Week 36 with Concentrations of Functional Dupilumab in Serum at Week 36 as a Predictor in Adult Participants with Moderate to Severe Bullous Pemphigoid on Active Drug (Study R668-BP-1902, CRAS, Primary Analysis)



n = Number of participants
Note: Placebo results are not shown. Concentrations below the LLOQ are set to 0 and missing concentrations are imputed with a LOCF approach. If a participant is missing sustained remission status at Week 36, they are excluded from this figure. Mean regression line - blue, confidence area around regression line - grey. Non-responders (0) and responders (1) individual concentration values are jittered. Means of response and 95% confidence intervals (green vertical lines) around the means are presented in the figures by exposure quartiles. These vertical lines are placed

at the means of interquartile ranges of an exposure on the x-axis.
Source: PTF 7.4.1.01

Figure 8. Mean (±SD) Percent Change from Baseline in BPDAI Activity Score by Nominal Time and Quartile of Functional Dupilumab Concentrations in Adult Participants with Moderate to Severe Bullous Pemphigoid (Study R668-BP-1902, CRAS, Primary Analysis)

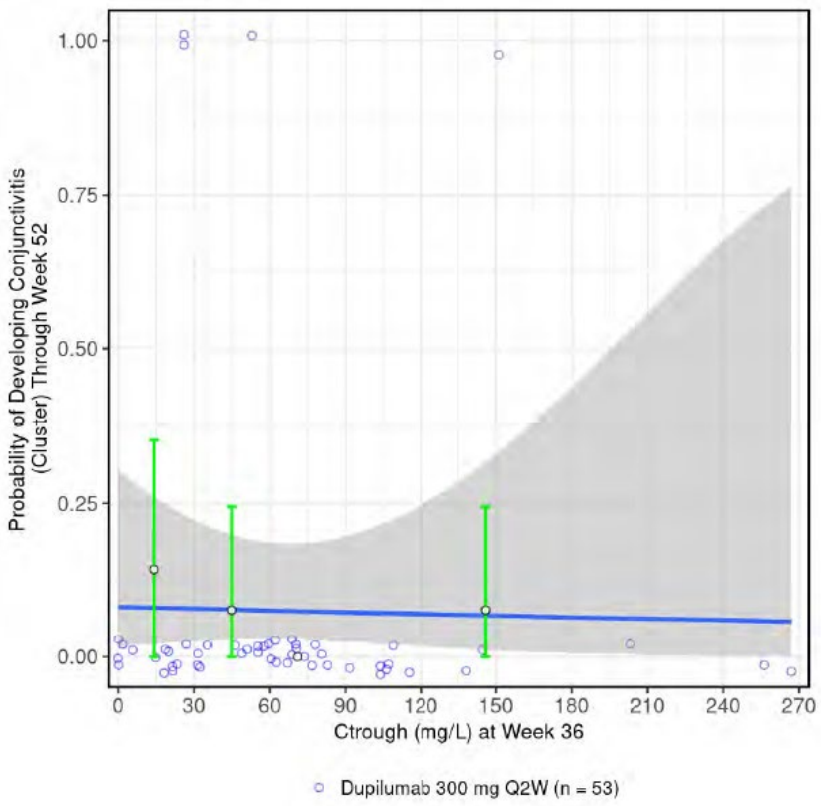


	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 24	Wk 32	Wk 36
Placebo	51	51	51	51	51	52	51	50	52	52	51	52
Q1	13	13	13	13	13	13	13	13	13	13	13	13
Q2	13	13	13	13	13	13	13	13	13	13	13	12
Q3	13	13	13	13	13	13	13	13	13	13	13	13
Q4	13	13	13	12	13	13	13	12	12	13	12	12

BPDAI = Bullous Pemphigoid Disease Area Index; Q1 = First quartile; Q2 = Second quartile; Q3 = Third quartile; Q4 = Fourth quartile; LOCF = Last observation carried forward
Note: This figure includes participants in the CRAS and placebo participants to show the full distribution. Concentrations below the LLOQ are set to 0 and missing concentrations are imputed with a LOCF approach. Subjects' Baseline and Week 2 concentration quartiles are set to their Week 4 concentration quartile because post-dose dupilumab sampling did not occur until Week 4. Response variables are imputed according to the primary analysis method. The table under the figure presents the number contributing to the statistics for the corresponding the quartile at each visit.
Source: PTF 7.4.2.03

Clinical response variables for **safety** included assessment of conjunctivitis (cluster terms) through week 52 and follow-up period up to data cutoff. Conjunctivitis (cluster terms) is based on the following PTs: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye inflammation, Eye irritation, and Giant papillary conjunctivitis.

Figure 9. Logistic Regression Relating Probability of Participants Developing Conjunctivitis (Cluster) Through Week 52 with Concentrations of Functional Dupilumab in Serum at Week 36 as a Predictor in Adult Participants with Moderate to Severe Bullous Pemphigoid on Active Drug (Study R668-BP-1902, PKAS, Primary Analysis)



n = Number of participants; LOCF = Last observation carried forward

Note: Only participants who had a Week 36 concentration within the analysis window as defined in the SAP are included. Concentrations below the LLOQ are set to 0 and missing concentrations are imputed with a LOCF approach. Mean regression line - blue, confidence area around regression line - grey. Participants who experienced (1) or did not experience (0) an event are jittered. Means of response and 95% confidence intervals (green vertical lines) around the means are presented in the figures by exposure quartiles. These vertical lines are placed at the means of interquartile ranges of an exposure on the x-axis.

Source: PTF 7.4.3.03

4.5. Immunogenicity

ADA was assessed in serum samples using a validated electrochemiluminescence bridging immunoassay. The presence of **NAb** was evaluated in ADA-positive serum samples only, using a validated competitive ligand-binding assay. The validated dupilumab ADA and NAb assay methods to assess immunogenicity were previously described in Module 2.7.1 in the initial adult AD and subsequent adult and adolescent asthma marketing applications.

The Anti-Drug Antibody Analysis Set included all participants who received any study drug (active or placebo, SAF) and had at least 1 non-missing ADA result following the first dose of study drug or placebo. Analysis is based on the treatment received.

The Neutralizing Antibody Analysis Set included all participants who received any study drug (active or placebo, SAF) and were negative in the ADA assay at all timepoints or had at least 1 non-missing post dose result in the NAb assay. Participants who were ADA negative were set to negative in the NAS.

Table 5. Summary of ADA Status, ADA Category, Maximum Titer Category, and NAb Status by Treatment Group in Adult Participants with Moderate to Severe Bullous Pemphigoid (Study R668-BP-1902, AAS)

ADA Status/Category Max. Titer Category NAb Status	Placebo n (%)	Dupilumab 300 mg Q2W n (%)	Overall n (%)
ADA			
ADA Analysis Set	50 (100%)	52 (100%)	102 (100%)
Negative	49 (98.0%)	50 (96.2%)	99 (97.1%)
Pre-existing Immunoreactivity	1 (2.0%)	0	1 (1.0%)
Treatment-Boosted Response	0	0	0
Treatment-Emergent Response	0	2 (3.8%)	2 (2.0%)
Persistent	0	0	0
Transient	0	0	0
Indeterminate	0	2 (3.8%)	2 (2.0%)
TE & TB Maximum Titer Category			
Low (<1,000)	0	1 (1.9%)	1 (1.0%)
Moderate (1,000 to 10,000)	0	1 (1.9%)	1 (1.0%)
High (>10,000)	0	0	0
NAb			
NAb Analysis Set	50 (100%)	52 (100%)	102 (100%)
NAb Negative	50 (100%)	50 (96.2%)	100 (98.0%)
NAb Positive	0	2 (3.8%)	2 (2.0%)

n = Number of participants; TE = Treatment-emergent; TB = Treatment-boosted
Note: Percentages are based on the ADA analysis set for ADA status, subcategories, and titer categories. Percentages are based on the NAb analysis set for NAb status.

4.6. Discussion on clinical pharmacology

This application is supported by data from a single phase 2/3 clinical trial: Study R668 BP 1902 informed on dupilumab trough concentrations, immunogenicity, and PD response on inflammatory biomarkers of adult patients with moderate-to-severe BP. Dupilumab concentration-response analyses for efficacy and safety in the BP population have been conducted. PK and PD results were compared with dupilumab data obtained in other indications with type 2 inflammation. Dupilumab concentration data were used for external validation in a previously established population PK model; the popPK model was further used for simulations on PK profiles and estimation of PK parameters in the BP population.

Study R668 BP 1902 utilized a dosing regimen with 300 mg dupilumab Q2W after a loading dose of 600 mg, which is already approved in other adult indications, namely AD, Asthma, and PN. Dupilumab PK has been characterized well in other type 2 inflammatory diseases of the skin and similarity of PK relationships across patient populations may be expected. Thus, the low number of subjects with very sparse PK sampling (pre-dose, weeks 4, 16, 36, 52, 64) may be sufficient in this case. At each

concentration timepoint investigated, a high inter-individual variability was seen with this low number of patients (53 patients treated with dupilumab). Data indicate that steady state is reached approximately at week 16 with a mean (SD) Ctrough of 67.9 (47.2) mg/L at, 71.9 (60.3) mg/L at week 36, and 78.5 (65.6) mg/L at week 52.

Mean dupilumab Ctroughs over 1 year of treatment were **compared with concentrations obtained in other already approved indications**. Throughout the investigated time period, Ctrough of dupilumab at steady-state for adults with BP was within the mean concentration range observed in other populations who received dupilumab 300 mg Q2W (with or without loading dose).

Dupilumab concentrations from study R668 BP 1902 were used for **external validation of a population PK model**. Given the already approved dosage scheme in other type 2 inflammatory diseases of the skin and the overall well characterized PK of dupilumab in adults, the impact of the pharmacometrics exercise and model-based conclusions is considered rather low. The popPK model was initially developed to describe dupilumab PK in healthy subjects and EoE patients. It included dupilumab concentration data from 6 clinical studies in healthy subjects and 3 clinical studies for patients with EoE, including adults, children, and adolescents as well as SC and IV dosing as fixed dose and weight-based. It was described as a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination, first-order SC absorption, covariate effects for body weight and albumin and transit compartments implemented in order to describe a lag in SC absorption. The visual predictive check (VPC) used the established model to plot the simulated concentration-time profile (median, 5th and 95th percentiles, with 90% CI) of dupilumab in the BP population and overlay the observed concentrations from Study R668-BP-1902. Dupilumab concentrations in BP patients were adequately predicted by the model. The popPK model was further used without any model adjustment to predict individual exposure metrics AUCtau, Cmax, and Ctrough of the BP participants in Study R668 BP 1902 as well as expected exposure in the BP population. The overall steady state Ctrough of 64.6 mg/L of the population simulation is comparable to steady state mean Ctroughs measured in study R668 BP 1902 and described previously with 300 mg dupilumab Q2W in steady state (SmPC: Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 55.3±34.3 mcg/mL to 81.5±43.9 mcg/mL for 300 mg administered Q2W).

The BP population in study R668 BP 1902 included a **wide range of body weights** (40-150 kg) and was of **higher age** (median [min-max]: 72.0 [48.0, 89.0]). As seen in other populations with fixed-dose regimens, increasing body weight was associated with decreased dupilumab concentrations. Body weight was comparable in the different age groups (age 18 < 65, 65 < 75, and ≥ 75 years) represented in study R668 BP 1902. In the popPK model, age was not a significant covariate on the PK of dupilumab after accounting for body weight. Thus, dupilumab exposure predictions (mean Ctrough,ss) were similar across age groups (≥18 to <65 years: 68.9 mg/L, ≥65 to <75 years: 63.6 mg/L, and ≥75 years: 63.1 mg/L).

No changes in the **SmPC wording** on description of dupilumab pharmacokinetics are planned, which can be agreed given the available information on PK in BP. The following sentence has been amended in the section on Elderly: "Of the 53 patients with BP exposed to dupilumab, a total of 40 were 65 years of age and older, including 22 patients 75 years of age and older. Efficacy and safety in this age group were similar to the overall study population." This does not raise concern.

With the single fixed-dosing regimen given, a **concentration-response analysis on efficacy and safety** was conducted. The concentration-response analysis for efficacy used concentration at week 36 as exposure metric and the primary endpoint (sustained remission of BP at week 36) as response variable. The low number of patients reaching this stringent endpoint (N=10) had dupilumab concentrations within the range of non-responders; A logistic regression showed no clear evidence of increasing response with increasing exposure. An additional analysis investigated mean percent change

from baseline in BPDAI activity score and dupilumab concentrations over time, with concentrations split in quartiles. There was no clear trend for higher efficacy with higher dupilumab concentration. For concentration-response analysis for safety, the probability of conjunctivitis was analyzed as response variable, with only 4 patients affected; A logistic regression showed no clear association. Overall, concentration-response analyses are considered to be of limited informative value due to low number of subjects with response for primary endpoint and TEAE PTs. Overall, analyses do not raise concern in terms of dosing regimen in BP.

Serum concentrations of thymus and activation regulated chemokine (TARC; CCL17) and IgE were analyzed as **exploratory PD endpoints**. As all patients were started on oral corticosteroids (OCS) at randomization and underwent protocol-defined OCS tapring, results need to be interpreted in this regard. While rebound of TARC is seen with OCS taper in the placebo group, no such effect is seen in the dupilumab group. Reductions from baseline in total IgE were observed in both treatment groups at week 4 with further decrease at week 16. At week 36, the decrease from baseline in total IgE was numerically greater in the dupilumab group (−83.02%) than in the placebo group (−56.24%). Overall, results on biomarkers investigated are considered supportive information only and do not raise concern.

In study R668 BP 1902 with concomitant OCS use in both treatment groups, the **incidence of anti-dupilumab antibodies** (ADAs) was low: 1 participant receiving placebo had pre-existing immunoreactivity (2.0%); 2 participants receiving dupilumab developed TE ADA (3.8%) at week 64 (latest timepoint investigated). Both patients with TE ADA were also nAB positive. However, dupilumab concentrations were within the range of ADA negative subjects. No TEAEs potentially associated with positive ADA status were determined in the 2 patients affected. Long-term treatment of dupilumab in BP is proposed; no immunogenicity data beyond 1 year of treatment are available. As immunogenicity in adult atopic dermatitis patients was investigated for up to 5 years with low incidence, this might be sufficient. SmPC wording on immunogenicity is agreed.

4.7. Conclusions on clinical pharmacology

Overall, the applied dosing regimen with 300 mg dupilumab Q2W after a loading dose of 600 mg is deemed appropriate for the adult BP population of higher age (median: 72 years). PK characteristics investigated by sparse sampling and additional popPK analysis were comparable to other adult populations with type 2 inflammation in already approved indications. Incidence of ADAs in study R668 BP 1902 was low and in line with previous dupilumab immunogenicity data.

5. Clinical efficacy

5.1. Dose response study

No dose response study was performed.

5.2. Main study

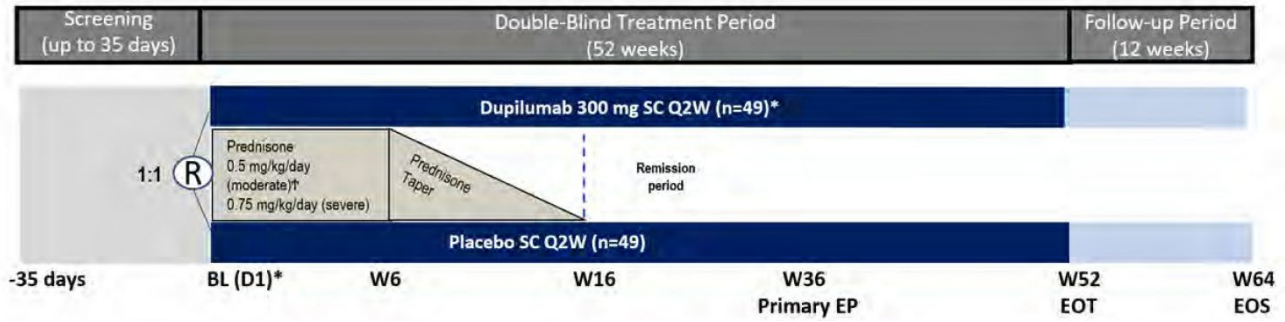
Study R668-BP-1902

The efficacy of dupilumab in the treatment of adults with BP was evaluated in a single pivotal phase 2/3 global, multicenter, randomized, double-blind, placebo controlled, parallel group study to assess the efficacy and safety of dupilumab in adults with BP.

Methods

The study included a 35-day screening period, a 52-week double-blind treatment period, and a 12-week post-treatment follow-up period.

Figure 10. Study Flow Diagram



All participants received background treatment OCS (prednisone or prednisolone). Tapering of OCS was to begin when there had been 2 weeks of control of disease activity. After the completed OCS taper a remission period followed in which patients were observed for BP relapses up to week 52 (sustained remission up to week 36 was evaluated as the primary endpoint).

Study participants

Key inclusion criteria were:

- Male or female, age 18 to 90 at the screening visit
- Confirmed diagnosis of BP based on histopathology, immunopathology, and serology by the baseline visit. Required for inclusion:
    - Compatible histopathologic findings on a skin biopsy specimen supporting a diagnosis of BP (eg, a subepidermal blister with eosinophils within the cleft, a mixed cellular inflammatory infiltrate that includes eosinophils)
    - Characteristic direct immunofluorescence findings on a skin biopsy specimen demonstrating linear IgG and/or C3 at the basement membrane zone

- At least 1 of the following serologic assessments:
  - Positive indirect immunofluorescence demonstrating IgG antibodies localizing to the roof (epidermal side) of split-skin substrate
  - Increased IgG serum antibody levels by immunoassay to BP antigens BP230 and/or BP180

- BPDAI activity score ≥24 at baseline and screening visits
- Baseline peak pruritus NRS score for maximum itch intensity ≥4

Key exclusion criteria were:

- Forms of pemphigoid other than classic BP (eg, Brunsting-Perry cicatricial pemphigoid, anti-p200 pemphigoid, epidermolysis bullosa acquisita, or BP with concomitant pemphigus vulgaris)
- Patients who are receiving treatments known to cause or exacerbate BP who have not been on a stable dose of these medications for at least 4 weeks prior to the screening visit
- Patients who ever have received treatment with an IL-4 or IL-13 antagonist
- Treatment with systemic corticosteroids within 7 days before the baseline visit
- Treatment with topical corticosteroids of medium potency or higher, topical calcineurin inhibitor, or topical crisaborole within 7 days before
- Treatment with non-steroidal immunosuppressive/immunomodulating drug(s) (eg, mycophenolate mofetil, azathioprine, or methotrexate) within 4 weeks before the baseline visit
- Initiation, discontinuation, or change in the dosage regimen of systemic antihistamines within 7 days before the baseline visit. Patients on a stable dose of systemic antihistamines for at least 7 days prior to the baseline visit may be included in the study; however, the dose of these medications should remain unchanged for the duration of the study.
- Treatment with BP-directed biologics as follows:
  - Any cell-depleting agents including but not limited to rituximab: within 12 months before the baseline visit, or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer
  - Other biologics (such as IL-5 inhibitors): within 5 half-lives or 16 weeks prior to the baseline visit, whichever is longer
  - Intravenous immunoglobulin within 16 weeks prior to the baseline visit

Treatments

Dupilumab

Dupilumab 300 mg SC q2w (initial loading dose: 600 mg SC on day 1)

Placebo

Matching placebo loading dose followed by q2w SC dosing

Background Medication

All participants, regardless of treatment assignment, were started on a standard regimen of OCS (prednisone or prednisolone) on day 1/baseline with the objective to taper OCS off by no later than week 16.

Specifically, participants with moderate BP (BPDAI activity score ≥24 and <60) received an initial dose of 0.5 mg/kg/day of prednisone (or prednisolone), and participants with severe BP (BPDAI activity score ≥60) received an initial dose of 0.75 mg/kg/day of prednisone (or prednisolone). Control of disease activity (defined as when new lesions ceased to form, and existing lesions began to heal) was expected to occur by 2 weeks after randomization with the above starting doses of OCS, but some patients may have taken longer; usually no longer than 4 weeks (Joly, 2002) (Simon, 2019).

Oral Corticosteroid Taper

Patients underwent a protocol-defined OCS tapering regimen as long as they maintain control of disease activity. The OCS taper employed a reduction by 0.1 mg/kg/day every two weeks until a dose of 0.1 mg/kg/day was reached, followed by a reduction to 0.05 mg/kg/day for two weeks and a final discontinuation of OCS treatment afterwards.

Rescue Medication

Rescue medications included super high potency topical corticosteroids group IV, systemic non-steroidal immunosuppressive drugs or immunomodulating biologics used for BP.

Participants who required doses greater than 0.75 mg/kg/day of prednisone (or prednisolone) and those who did not achieve control of disease activity by week 4 could receive rescue treatment per investigator's discretion.

During the OCS taper period, if a participant experienced a loss of control of disease activity (ie, new lesions (eg. blisters, urticarial plaques began to form and existing lesions did not heal), the OCS dose could be increased to the dose level where there was control of disease activity. During taper, participants were permitted to increase their OCS once, with any subsequent increases being considered rescue therapy. If a participant failed to complete the OCS taper a second time were considered for rescue treatment as per investigator's discretion.

After tapering off OCS, participants who experience a relapse could also be rescued, including with re-initiation of OCS. A BP relapse was defined as the appearance of 3 or more new lesions a month (blisters, eczematous lesions, or urticarial plaques) or at least 1 large (>10 cm diameter) eczematous lesion or urticarial plaque that does not heal within 1 week.

Participants were allowed to continue study treatment if rescued with topical corticosteroids or OCS.

If a patient received rescue treatment with a systemic non-steroidal immunosuppressive drug or immunomodulating biologic (including, but not limited to, omalizumab, rituximab, mycophenolate-mofetil, azathioprine, methotrexate), study treatment was to be permanently discontinued.

Objectives

Primary objective:

- To demonstrate that dupilumab is superior to placebo in achieving sustained remission off OCS in participants with BP

Secondary objectives

- To evaluate the OCS-sparing effects of dupilumab in participants with BP
- To evaluate the effect of dupilumab on itch in participants with BP
- To evaluate the effects of dupilumab on health-related quality of life measures in participants with BP
- To evaluate the effect of dupilumab in circulating BP180 and BP230 autoantibody titers
- To assess the safety and tolerability of dupilumab administered to participants with BP
- To characterize the trough concentrations of functional dupilumab over time following administration of dupilumab in participants with BP
- To assess the immunogenicity of dupilumab in participants with BP over time

Outcomes/endpoints

Primary endpoint:

- Proportion of participants achieving sustained remission at week 36, defined as meeting all of the following requirements:
    - Achievement of complete remission and off OCS no later than week 16 after randomization (complete remission was defined as absence of new lesions and epithelialization of old lesions)
    - Absence of disease relapse from the time the participant has completed the OCS taper (no later than week 16 after randomization) to week 36
      (relapse was defined as the appearance of 3 or more new lesions a month [blisters, eczematous lesions, or urticarial plaques] or at least 1 large [>10 cm diameter] eczematous lesion or urticarial plaque that does not heal within 1 week)
    - Absence of need for rescue therapy during the 36-week double-blind treatment period (rescue therapy includes increase of OCS dose during the taper, re-initiation of OCS after completion of the OCS taper, or initiation of any BP-directed therapy).

Secondary endpoints (multiplicity controlled):

- Percent change in BPDAI activity score from baseline to week 36
- Time to first use of rescue medication (up to week 36)
- Proportion of participants with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36
- Percent change in weekly average of daily peak pruritus NRS from baseline to week 36
- Total cumulative dose of OCS from baseline to week 36
- Duration of complete remission while not requiring OCS (up to week 36)
- Proportion of participants who achieve a reduction in BPDAI activity score of at least 90% from baseline to week 36
- Change from baseline to week 36 in percent BSA of BP involvement
- Change in BP180 autoantibody (IgG) titers from baseline to week 36

- Change in ABQOL from baseline to week 36

Sample size

The sample size calculation of the study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the primary endpoint at week 36 for the patients achieving sustained remission. Assuming 35% of the placebo group achieve the primary endpoint, approximately 98 randomized patients (49 per arm) would yield >90% power to detect a 40% difference in the primary endpoint response with a 2-sided significance level of α=0.01 using Fisher's exact test. The same sample size would provide >90% power with 2-sided significance level of α=0.05 taking into account a dropout rate of approximately 20%.

The placebo rate of 35% is based on publications (Simon, 2019; Joly, 2009) and expert opinion. The 40% treatment difference between dupilumab and placebo is based on discussion with experts and corroborated with publications (Abdat, 2020; Simon, 2019).

Approximately 10% of the study population is planned to be from Japan.

Randomisation

Patients were randomized in a 1:1 ratio to receive either a loading dose of 600 mg SC followed by 300 mg dupilumab every 2 weeks (q2w), or a matching placebo loading dose and SC placebo injections q2w, according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

Randomization was stratified by baseline disease severity (moderate [BPDAI score =24 and <60] vs. severe [BPDAI =60]), region (North America vs. Europe vs. Japan) and prior corticosteroid/ immuno-suppressant use (Yes vs. No). Approximately 10% of the study population was planned to be from Japan. Patients from study sites in Japan were not stratified.

All patients received a standard regimen of OCS (prednisone or prednisolone) on day 1/baseline visit to obtain control of disease. Specifically, patients with moderate BP (BPDAI activity score ≥24 and <60) received 0.5 mg/kg/day of prednisone (or prednisolone) and patients with severe BP (BPDAI activity score ≥60) received 0.75 mg/kg/day of prednisone (or prednisolone).

Blinding (masking)

Study patients, the principal investigators, and study site personnel were to remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site were to remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a medication numbering system were to be used. In order to maintain the blind, lists linking these codes with product lot numbers were not to be accessible to individuals involved in study conduct.

Anti-drug antibody, drug concentration results, and biomarker results (e.g., TARC) were not be communicated to the sites, and the sponsor's blinded operational team was not have access to results associated with patient identification until after the database is locked.

Statistical methods

Analysis of primary endpoint

The primary analysis of the proportion of patients achieving sustained remission at week 36 was performed using the stratified MH method, adjusting for baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/ immuno-suppressant use (Yes versus No). The estimate of the MH-weighted risk difference and corresponding 2-sided Wald 95% CI using the Sato variance was to be presented along with the p-value. An exact method such as Barnard's exact test for p-value and 2-sided Miettinen and Nurminen 95% CI (based on the method of Lu and Guo, 2021) for the risk difference was to be used if the expected frequencies in all cells are not at least 5.

Primary estimand

The primary estimand for the primary endpoint is summarized in below. Sensitivity analyses (including tipping point analyses) to determine the patient's status at week 36 to assess the robustness of the primary efficacy analysis with regard to handling of missing data were defined in the SAP.

Table 6. Summary of Primary Estimand for Primary Endpoint

Population	Treatment	Endpoint	Intercurrent Events and Missing Data Handling	Population-Level Summary
Patients with BP	• Dupilumab • Placebo	Achievement of sustained remission at Week 36.	Intercurrent Events: • Rescue treatment: Patients will be considered as non-responders after such events (Composite Strategy). • Treatment discontinuation: Data collected after the patient discontinued treatment will be included in the analysis (Treatment Policy Strategy). Missing data: Applying the above two rules for intercurrent events, if there are still missing data and the observed data cannot determine that the patient is a non-responder, the handling methods are as follows: • Patient will be considered as a non-responder if the patient's data are missing at week 36 due to discontinuation from the study caused by lack of efficacy, treatment-related AEs or death. • For any other missing data, including missing data due to COVID-19, MI approach will be used.	Difference in the proportion of patients with sustained remission at Week 36 between treatment groups.

For missing data, multiple imputation (MI) was to be used with a pre-specified random seed to generate 50 complete datasets based on patients who have non-missing sustained remission outcome at week 36. The MI was based on a logistic regression model with treatment group as an independent variable, baseline disease severity, region, and prior corticosteroid/immunosuppressant use as covariates, and status of achieving sustained remission at week 36 as the response variable in the logistic regression model. Each of the imputed complete datasets was to be analysed by the MH test, and Rubin's rules was to be applied to combine the estimates and perform statistical inference across imputations.

Key secondary endpoints and estimands

Secondary efficacy endpoints that measure binary response at week 36 were to be analysed in the same fashion as the primary endpoint including the method(s) to handle missing data. Multiple imputation was to be based on the underlying continuous variables (i.e., weekly average of daily peak pruritus NRS and BPDAI activity score).

The endpoint of the total cumulative dose of OCS from baseline to week 36 was to be analysed using an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline OCS dose included in the model as covariates. The treatment group difference was to be tested at the 2-sided 5% significance level. The intercurrent event of non-OCS systemic rescue treatment was treated by imputing days after non-OCS systemic rescue treatment using WOCF including baseline (composite strategy), and treatment discontinuation by including data collected after the patient discontinued treatment in the analysis (treatment policy strategy). Missing values subsequent to discontinuation from the study until week 36 (Day 253, inclusive) was to be imputed with the daily average OCS dose of the other patients who had completed the week 36 visit in the same treatment arm; the daily average was to be computed using the daily records from the day after a given patient discontinues from the study through study Day 253.

Continuous secondary efficacy endpoints (e.g., percent change in weekly average of daily peak pruritus NRS from baseline to week 36 and percent change in BPDAI activity score from baseline to week 36) were to be analysed using an analysis of covariance model with treatment group, randomization stratification factors (baseline disease severity [moderate versus severe BP], region [North America versus Europe versus Japan] and prior corticosteroid/immunosuppressant use [Yes versus No]) and relevant baseline measurement included in the model. To account for the impact of rescue treatment on the efficacy effect, patients' efficacy data through week 36 after the rescue treatment use was to be set to missing and imputed with the worst value from the closest visit immediately prior to rescue medication use (scheduled visit including baseline or unscheduled visit), on the visit of initiation of rescue treatment or afterwards up to and including week 36. Data are captured at visits; therefore, the worst value around and after the time of rescue treatment was to be carried forward from one of the following until week 36 (whichever value is worst): the visit immediately prior to starting rescue treatment; or the visit when rescue treatment was started; or the visits after rescue treatment was started. The missing data for continuous endpoints (except for the endpoint of the total cumulative dose of OCS), was to be imputed by the hybrid approach, specifically the worst value/Worst Observation Carried Forward-Multiple Imputation (worst/WOCF-MI) approach, where worst value/WOCF was to be used for intercurrent event/missing data due to rescue treatment/study discontinuation due to treatment-related AEs, death, and lack of efficacy, and the MI approach was to be used for missing data due to other reasons.

Time to first use of rescue medication was to be analysed by a Cox proportional hazards model including treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/immunosuppressant use (Yes versus No) in the model as covariates. Patients who did not use rescue medication up to week 36 (Day 253, inclusive) were to be censored at Day 253. The hazard ratio between the two treatment groups were to be reported with the 95% confidence interval and p-value. Data collected after the patient discontinued treatment was to be included in the analysis (treatment policy strategy). Study discontinuation due to lack of efficacy, treatment-related AEs, or death was to be considered as having used rescue medication at the time of study discontinuation. Study discontinuation due to any other reasons was to be censored at the date of study discontinuation.

Multiplicity control

A hierarchical testing procedure was defined in the SAP. Each hypothesis was to be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchy is shown in Table 7. Hierarchical order

Table 7. Hierarchical order

	Endpoints	Testing Order
Primary Endpoint	Proportion of patients achieving sustained remission at week 36	1
Key Secondary Endpoints	Percent change in BPDAI activity score from baseline to week 36	2
	Time to first use of rescue medication (up to week 36)	3
	Proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥4 from baseline to week 36	4
	Percent change in weekly average of daily peak pruritus NRS from baseline to week 36	5
	Total cumulative dose of OCS from baseline to week 36	6
Other Secondary Endpoints	Duration of complete remission while not requiring OCS (up to week 36)	7
	Proportion of patients who achieve a reduction in BPDAI activity score of at least 90% from baseline to week 36	8
	Change from baseline to week 36 in percent BSA of BP involvement	9
	Change in BP180 autoantibody (IgG) titers from baseline to week 36	10
	Change in ABQOL from baseline to week 36	11

Key changes to SAP in the conduct of study

- **Amendment 1 (11 Jun 2020):** A purpose of this amendment was to address regulatory authority feedback regarding study design. The significance level was reduced from 5% to 1% and the number of patients to be enrolled in the study has been consequently increased. The duration of the double-blind treatment period has been extended from 36 to 52 weeks.
- **Amendment 2 (22 Apr 2021):** A purpose of this amendment was to add estimands for the statistical analyses of primary and key secondary efficacy endpoints.
- **Amendment 3 (04 Mar 2024):** A purpose of this amendment was to modify the statistical significance level (from 1% to 5%), add a new secondary endpoint for efficacy (time to first use of rescue medication), modify 2 existing secondary endpoints for efficacy, and further clarify the corresponding efficacy analyses.
- **SAP Amendment 1** (01 Aug 2024):
    - **Changes from Protocol Amendment 3 in the SAP (Amendment 1):** The primary analysis method for the primary endpoint was changed from the CMH method for odds ratios to the MH method for differences in proportions. The primary analysis method for the assessment of the total cumulative dose of OCS was changed from the Wilcoxon rank-sum test to an ANCOVA model. The Wilcoxon rank-sum test was to be performed as a supportive analysis.

Results

Participant flow

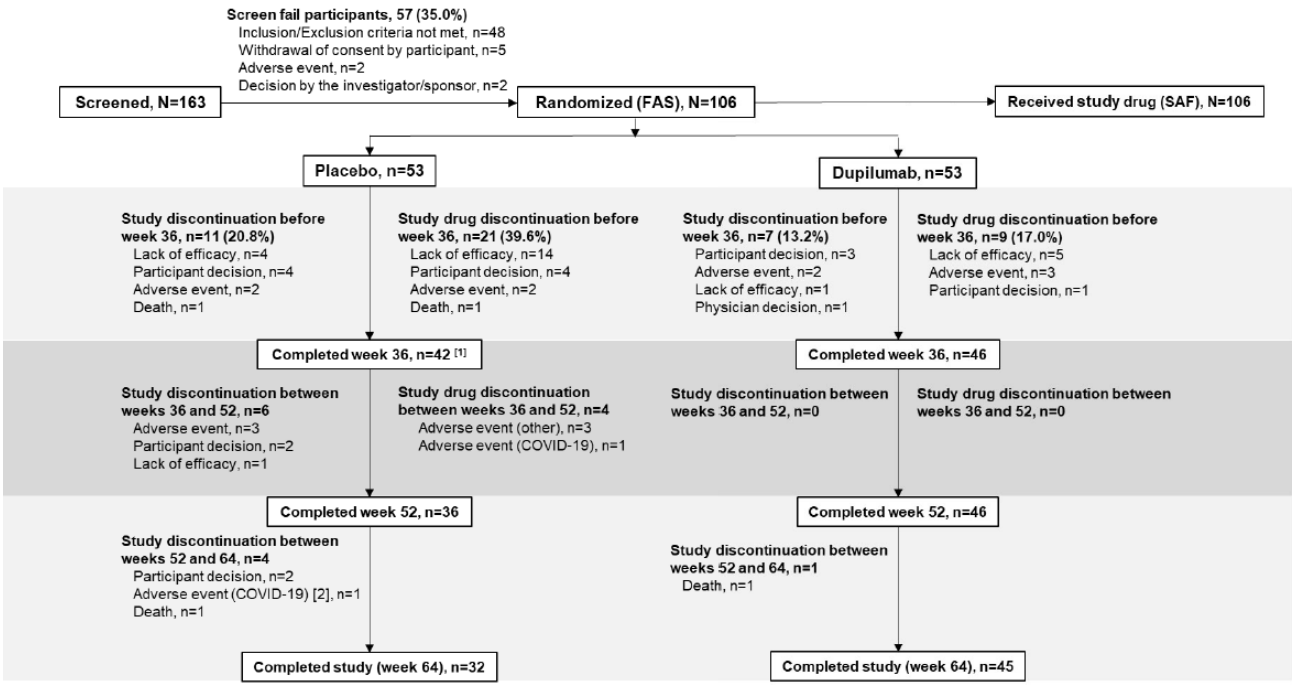
Overall, 38 study centres randomized participants: 9 in Germany, 8 in the US, 5 in France, 5 in Japan, 3 in Poland, 2 in Australia, 2 in Israel, 2 in Spain, and 2 in Taiwan.

A total of 163 participants were screened, and 35.0% (57/163) of participants failed screening. The most frequently reported reason for screen failure was "inclusion/exclusion criteria not met" (84.2% (48/57).

Of the 106 randomized participants, all received study intervention. There was higher number of study drug discontinuations or discontinuations from the study in the placebo group which was in part driven by a higher number of participants with "lack of efficacy".

At the time of data cutoff, all randomized participants (106/106) had either completed visits through week 52 (77.4%; 82/106) or discontinued from the study prior to week 52 (22.6%; 24/106). A total of 60.4% (32/53) of participants in the placebo group and 84.9% (45/53) of participants in the dupilumab group had also completed the follow-up period through week 64. No participant is ongoing.

Figure 11. Participant Disposition



[1] At the time of the Primary Analysis CSR Amendment 1 data cutoff date, 1 participant in the placebo group discontinued study drug before week 36 and remained on study until their early termination visit. The early termination visit occurred after the data cutoff date (but prior to the database lock date) for the Primary Analysis CSR Amendment 1, and therefore, this participant was counted as ongoing in the study before weeks 36, 52, and 64. As of the database lock date for this CSR addendum, the participant had completed the early termination visit and is now considered as having completed the study through week 36 and discontinued before week 52.
[2] At the time of the Primary Analysis CSR Amendment 1 data cutoff date, there were 2 participants in the placebo group who were considered as having discontinued the study between week 52 and week 64 due to death. As of the database lock date for this CSR addendum, follow-up information was received on 1 of these 2 participants, and the disposition status for this participant was updated to study discontinuation due to COVID-19-related AE.

Abbreviations: FAS=full analysis set; SAF=safety analysis set.

Recruitment

First participant enrolled:	28 Oct 2020
Study Completion (last participant visit):	05 Jan 2025
The primary analysis data cut-off:	18 Feb 2025

Conduct of the study

Protocol amendments

The protocol was amended 3 times. With amendment 1 (18 Oct 2019), the statistical significance level was changed from 0.05 (2-sided) to 0.01 (2-sided). As a result, the approximate number of patients to be randomized was increased from 40 per arm to 49 per arm for a total enrollment of approximately 98 patients to attain at least 90% power. Additional exclusion criteria were incorporated. Other minor changes were made for clarification and to protect patient safety and data integrity during the COVID-19 pandemic. Amendment 2 (11 Jun 2020) added flexibility for the visit options (eg, telemedicine) in view of the COVID-19 pandemic, updated the patient eligibility requirements (eg. wash-out periods and stable dose requirements for concomitant treatments), and added estimands for the statistical analyses of primary and key secondary efficacy endpoints. With amendment 3 (03 Mar 2024), the statistical significance level was again changed from 0.01 to 0.05. Time to first use of rescue medication (up to week 36)" was new key secondary endpoint for efficacy. The imputation strategy for continues endpoints (WOCF from closes visits to rescue treatment use) was further clarified.

COVID-19 Pandemic

The study was conducted partly during the COVID-19 pandemic. The sponsor made a decision that this study would continue enrollment based on the assessment that the study could be conducted without potentially negatively impacting participant safety, data integrity, or compliance with recent Regulatory Guidance.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight required implementation of temporary or alternative mechanisms. Alternate mechanisms employed included, but were not limited to, virtual visits and home visits by skilled staff.

Protocol deviations

A total of 138 important protocol deviations were reported from 67/106 participants (63.2%). The important protocol deviations categories that were reported in the highest proportions of participants were "received an excluded concomitant treatment" (26/106; 24.5%) and "inadequate informed consent administration" (24/106; 22.6%). The use of excluded medications in these categories were generally balanced between the treatment groups.

<u>Received an Excluded Concomitant Treatment</u>
To assess if any of these medications had an impact on the efficacy outcome, the responder status for sustained remission at week 36 (primary endpoint) of these 26 participants. Of the 26 participants, 24 participants were considered non-responders for the primary endpoint. The remaining 2 participants (both in the dupilumab group) only had a short duration of corticosteroid treatment and were considered responders for the primary endpoint. One participant received prednisone 20 mg twice daily for a short period of time (6 days; study days 233 to 238) for the treatment of an asthma exacerbation, while the other participant used potent topical steroids for 3 days (study days 214 to 216) locally for an AE (mosquito bite).

A total of 7 patients (6.6%) (placebo: n=3; dupilumab: n=4) of participants received a highly potent (class IV) topical steroid for non-rescue reasons or without meeting protocol criteria for rescue. 4 of these 7 participants received highly potent topical corticosteroids for the treatment of a TEAE. The remaining 3 participants (placebo: n=1; dupilumab 300 mg Q2W: n=2) received highly potent topical corticosteroids with the reason recorded as for BP/rescue and were consequently considered as non-responders for the primary endpoint analysis.

Inadequate Informed Consent Administration

There were 24 participants (placebo: n=9; dupilumab 300 mg Q2W: n=15) with at least 1 important protocol deviation of inadequate informed consent administration. Importantly, no protocol deviations were identified for a missing initial consent prior to initiating study procedures. Important protocol deviations for inadequate informed consent administration included missed consent for the optional genomic or FBR samples, use of an outdated version of the ICF signed at screening, no re-consented at first opportunity. Sites were re-trained on correct consent processes.

Received Wrong Treatment or Incorrect Dose

Overall, 17 participants (placebo: n=10; dupilumab: n=7) had at least 1 important protocol deviation in the category of received wrong treatment or incorrect dose; all protocol deviations in this category were related to an incorrect initial starting background OCS dose or to the OCS taper not following the protocol-specified taper regimen. There were 8 participants (placebo: n=6; dupilumab: n=2) with an OCS starting dose that was lower as specified in the protocol based on their baseline BPDAI disease severity. Of these participants, 6 achieved initial disease control by week 4 (placebo: n=4; dupilumab 300 mg Q2W: n=2). There were 9 participants (placebo: n=4; dupilumab: n=5) who started to taper the OCS prior to the week 4 visit.

Baseline data

Demographics

Demographic characteristics of participants, including age, race, ethnicity, geographical region, and weight were generally balanced across the 2 treatment groups. The placebo group had a higher percentage of male participants than the dupilumab 300 mg Q2W group (54.7% [29/53] vs 39.6% [21/53]). Overall, most participants were White (67.9%; 72/106) and not Hispanic or Latino (80.2%; 85/106). The mean (SD) age of the enrolled study population was 71.3 (9.72) years, with 77.4% of participants aged ≥65 years and 41.5% of participants aged ≥75 years.

Demographic characteristics of the enrolled participants were generally consistent with published literature for the BP population (Chung, 2022) (Hübner, 2016) (Langan, 2008).

Table 8. Demographics (FAS)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Age (years)			
n	53	53	106
Mean (SD)	71.5 (9.52)	71.2 (10.01)	71.3 (9.72)
Median	73.0	72.0	72.0
Q1 : Q3	66.0 : 78.0	65.0 : 79.0	65.0 : 79.0
Min : Max	42 : 87	48 : 89	42 : 89
Age group, n (%)			
<65 years	11 (20.8%)	13 (24.5%)	24 (22.6%)
≥65 years	42 (79.2%)	40 (75.5%)	82 (77.4%)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
≥65 to <75 years	20 (37.7%)	18 (34.0%)	38 (35.8%)
≥75 years	22 (41.5%)	22 (41.5%)	44 (41.5%)
Ethnicity, n (%)			
Hispanic or Latino	3 (5.7%)	0	3 (2.8%)
Not Hispanic or Latino	42 (79.2%)	43 (81.1%)	85 (80.2%)
Unknown	1 (1.9%)	2 (3.8%)	3 (2.8%)
Not Reported	7 (13.2%)	8 (15.1%)	15 (14.2%)
Race, n (%)			
White	37 (69.8%)	35 (66.0%)	72 (67.9%)
Black or African American	1 (1.9%)	1 (1.9%)	2 (1.9%)
Asian	7 (13.2%)	9 (17.0%)	16 (15.1%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	2 (3.8%)	0	2 (1.9%)
Not Reported	6 (11.3%)	8 (15.1%)	14 (13.2%)
Region (IWRS), n (%) [1]			
North America	12 (22.6%)	12 (22.6%)	24 (22.6%)
Europe	35 (66.0%)	37 (69.8%)	72 (67.9%)
Japan	6 (11.3%)	4 (7.5%)	10 (9.4%)
Region, n (%) [1]			
North America	12 (22.6%)	12 (22.6%)	24 (22.6%)
Europe	34 (64.2%)	32 (60.4%)	66 (62.3%)
Asia	7 (13.2%)	9 (17.0%)	16 (15.1%)
Country, n (%)			
Australia	3 (5.7%)	2 (3.8%)	5 (4.7%)
France	7 (13.2%)	8 (15.1%)	15 (14.2%)
Germany	18 (34.0%)	16 (30.2%)	34 (32.1%)
Israel	2 (3.8%)	3 (5.7%)	5 (4.7%)
Japan	6 (11.3%)	4 (7.5%)	10 (9.4%)
Poland	2 (3.8%)	2 (3.8%)	4 (3.8%)
Spain	2 (3.8%)	1 (1.9%)	3 (2.8%)
Taiwan	1 (1.9%)	5 (9.4%)	6 (5.7%)
United States	12 (22.6%)	12 (22.6%)	24 (22.6%)
Sex, n (%)			
Male	29 (54.7%)	21 (39.6%)	50 (47.2%)
Female	24 (45.3%)	32 (60.4%)	56 (52.8%)
Height (cm)			
n	53	53	106
Mean (SD)	166.66 (10.275)	166.36 (11.901)	166.51 (11.066)
Median	168.50	167.00	168.00
Q1 : Q3	158.00 : 174.00	156.00 : 174.00	157.00 : 174.00
Min : Max	147.1 : 188.0	140.0 : 200.0	140.0 : 200.0
Weight (kg)			
n	53	53	106
Mean (SD)	78.35 (15.766)	76.57 (20.439)	77.46 (18.187)
Median	79.00	75.00	76.00

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Q1 : Q3	68.90 : 90.00	63.50 : 85.00	65.30 : 90.00
Min : Max	39.8 : 118.0	40.4 : 150.0	39.8 : 150.0
Weight group, n (%)			
<60 kg	6 (11.3%)	9 (17.0%)	15 (14.2%)
≥60 to <90 kg	33 (62.3%)	31 (58.5%)	64 (60.4%)
≥90 kg	14 (26.4%)	13 (24.5%)	27 (25.5%)
BMI (kg/m^2)			
n	53	53	106
Mean (SD)	28.27 (5.774)	27.51 (6.141)	27.89 (5.944)
Median	27.60	27.20	27.20
Q1 : Q3	24.80 : 32.00	23.20 : 30.20	23.50 : 31.20
Min : Max	18.4 : 46.7	17.9 : 48.8	17.9 : 48.8
BMI group, n (%)			
<15 kg/m^2	0	0	0
≥15 to <25 kg/m^2	15 (28.3%)	17 (32.1%)	32 (30.2%)
≥25 to <30 kg/m^2	21 (39.6%)	22 (41.5%)	43 (40.6%)
≥30 kg/m^2	17 (32.1%)	14 (26.4%)	31 (29.2%)

Percentages are based on the number of randomized participants in each treatment group as denominator.
[1] Regions for stratification were as follows: North America vs. Europe (including Australia, Israel and Taiwan) vs. Japan. Regions used for subgroup analyses were as follows: North America vs. Europe (including Australia and Israel) vs. Asia (Taiwan and Japan).
Abbreviations: BMI=body mass index; FAS=full analysis set; IWRS=interactive web response system; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.1.2.1

Baseline Disease Characteristics

Overall, the mean (SD) age at BP onset was 70.7 (9.77) years and the mean (SD) duration of disease at baseline was 0.95 (1.591) years, with 65.1% of participants having new-onset disease (defined as those patients not classified as relapsed disease based on the investigator's judgement). Overall, mean (SD) BPDAI activity score at baseline was 60.5 (29.99). All (106/106) participants had cutaneous blisters/erosions, 95.3% (101/106) of participants had cutaneous urticaria/erythema and 27.4% (29/106) of participants had mucosal blisters/erosions at baseline. Per IWRS, 58.5% (62/106) of participants previously received corticosteroids or immunosuppressants and 34.0% (36/106) had severe baseline disease severity. Mean (SD) BSA affected by BP was 30.8% (20.37%), with 58.5% (62/106) of participants experiencing >50 erosions/blisters at baseline. Mean (SD) baseline peak pruritus NRS score was 7.5 (1.59), indicating severe symptoms (peak pruritus NRS range from 0 to 10; higher scores indicate worse pruritus). Participants also reported that the disease had a substantial impact on QoL, with a mean (SD) ABQOL score of 22.3 (9.45) (scale of 0 to 51; a higher score reflects worse QoL).

Table 9. Baseline Disease Characteristics (FAS)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Duration of bullous pemphigoid (years)			
n	53	53	106
Mean (SD)	0.94 (1.769)	0.96 (1.408)	0.95 (1.591)
Median	0.30	0.50	0.30
Q1 : Q3	0.10 : 0.70	0.20 : 1.10	0.20 : 0.80
Min : Max	0.0 : 8.9	0.0 : 7.5	0.0 : 8.9

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Status of disease at baseline, n (%) [1]			
New onset	34 (64.2%)	35 (66.0%)	69 (65.1%)
Relapsed active disease	19 (35.8%)	18 (34.0%)	37 (34.9%)
Age at bullous pemphigoid onset (years)			
n	53	53	106
Mean (SD)	70.8 (9.54)	70.6 (10.09)	70.7 (9.77)
Median	72.0	71.0	72.0
Q1 : Q3	65.0 : 78.0	63.0 : 78.0	64.0 : 78.0
Min : Max	41 : 87	47 : 89	41 : 89
Prior corticosteroid/immunosuppressant use (IWRS), n (%)			
Yes	32 (60.4%)	30 (56.6%)	62 (58.5%)
No	21 (39.6%)	23 (43.4%)	44 (41.5%)
Baseline BPDAI activity score			
n	53	53	106
Mean (SD)	58.5 (28.47)	62.5 (31.58)	60.5 (29.99)
Median	57.0	56.0	57.0
Q1 : Q3	35.0 : 72.0	42.0 : 74.0	39.0 : 72.0
Min : Max	24 : 144	25 : 162	24 : 162
Baseline BPDAI cutaneous blisters/erosions score			
n	53	53	106
Mean (SD)	29.6 (16.66)	35.9 (22.13)	32.7 (19.75)
Median	27.0	30.0	27.0
Q1 : Q3	21.0 : 37.0	22.0 : 47.0	21.0 : 40.0
Min : Max	2 : 82	3 : 104	2 : 104
Baseline BPDAI cutaneous blisters/erosions score category, n (%)			
0	0	0	0
≥1	53 (100%)	53 (100%)	106 (100%)
Baseline BPDAI cutaneous urticaria/erythema score			
n	53	53	106
Mean (SD)	27.9 (20.47)	25.0 (16.45)	26.5 (18.54)
Median	26.0	21.0	23.0
Q1 : Q3	15.0 : 34.0	15.0 : 30.0	15.0 : 33.0
Min : Max	0 : 110	0 : 77	0 : 110
Baseline BPDAI cutaneous urticaria/erythema score category, n (%)			
0	4 (7.5%)	1 (1.9%)	5 (4.7%)
≥1	49 (92.5%)	52 (98.1%)	101 (95.3%)
Baseline BPDAI mucosal blisters/erosions score			
n	53	53	106
Mean (SD)	1.0 (3.94)	1.6 (3.49)	1.3 (3.71)
Median	0.0	0.0	0.0
Q1 : Q3	0.0 : 0.0	0.0 : 1.0	0.0 : 1.0

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Min : Max	0 : 27	0 : 15	0 : 27
Baseline BPDAI mucosal blisters/erosions score category, n (%)			
0	42 (79.2%)	35 (66.0%)	77 (72.6%)
≥1	11 (20.8%)	18 (34.0%)	29 (27.4%)
Baseline disease severity (IWRS), n (%)			
Moderate (BPDAI activity score ≥24 to <60)	36 (67.9%)	34 (64.2%)	70 (66.0%)
Severe (BPDAI activity score ≥60)	17 (32.1%)	19 (35.8%)	36 (34.0%)
Baseline BPDAI pruritus score			
n	52	53	105
Mean (SD)	23.0 (4.26)	22.5 (5.21)	22.7 (4.75)
Median	24.0	23.0	23.0
Q1 : Q3	20.5 : 26.0	19.0 : 27.0	20.0 : 26.0
Min : Max	14 : 30	9 : 30	9 : 30
Baseline peak pruritus NRS score [1]			
n	53	51	104
Mean (SD)	7.4 (1.54)	7.6 (1.64)	7.5 (1.59)
Median	7.8	7.7	7.7
Q1 : Q3	6.3 : 8.5	6.6 : 9.0	6.4 : 8.8
Min : Max	5 : 10	4 : 10	4 : 10
Baseline skin pain NRS score [1]			
n	53	51	104
Mean (SD)	5.8 (2.52)	6.4 (2.22)	6.1 (2.38)
Median	5.7	7.0	6.6
Q1 : Q3	3.7 : 8.0	5.1 : 8.0	4.4 : 8.0
Min : Max	0 : 10	1 : 10	0 : 10
Baseline sleep quality NRS score [1]			
n	53	51	104
Mean (SD)	5.1 (1.93)	4.0 (1.98)	4.6 (2.02)
Median	5.0	3.7	4.4
Q1 : Q3	3.7 : 6.6	2.6 : 5.1	3.1 : 5.7
Min : Max	1 : 8	0 : 9	0 : 9
Baseline BSA affected by bullous pemphigoid (%)			
n	53	53	106
Mean (SD)	32.2 (21.63)	29.4 (19.13)	30.8 (20.37)
Median	29.0	25.5	26.5
Q1 : Q3	16.0 : 47.0	12.5 : 46.0	13.0 : 46.0
Min : Max	0 : 99	4 : 69	0 : 99
Baseline ABQOL score			
n	47	48	95
Mean (SD)	21.7 (9.12)	22.9 (9.82)	22.3 (9.45)
Median	21.0	24.5	23.0
Q1 : Q3	15.0 : 29.0	15.5 : 32.0	15.0 : 31.0
Min : Max	2 : 39	2 : 38	2 : 39

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Baseline EQ-5D-3L utility index			
n	53	53	106
Mean (SD)	0.4184 (0.39986)	0.4479 (0.37326)	0.4332 (0.38522)
Median	0.5870	0.5870	0.5870
Q1 : Q3	0.0880 : 0.7270	0.0880 : 0.7960	0.0880 : 0.7270
Min : Max	-0.429 : 1.000	-0.594 : 1.000	-0.594 : 1.000
Baseline EQ-VAS score			
n	52	53	105
Mean (SD)	46.9 (26.93)	50.3 (22.98)	48.6 (24.95)
Median	50.0	50.0	50.0
Q1 : Q3	23.5 : 70.0	35.0 : 70.0	30.0 : 70.0
Min : Max	0 : 95	0 : 95	0 : 95
Baseline PGADS, n (%)			
No symptoms	1 (1.9%)	0	1 (0.9%)
Mild symptoms	0	0	0
Moderate symptoms	19 (35.8%)	19 (35.8%)	38 (35.8%)
Severe symptoms	18 (34.0%)	19 (35.8%)	37 (34.9%)
Very severe symptoms	15 (28.3%)	15 (28.3%)	30 (28.3%)
Baseline erosions/blisters count, n (%)			
0	2 (3.8%)	3 (5.7%)	5 (4.7%)
1-2	1 (1.9%)	0	1 (0.9%)
3-5	0	3 (5.7%)	3 (2.8%)
6-10	2 (3.8%)	0	2 (1.9%)
10-20	6 (11.3%)	3 (5.7%)	9 (8.5%)
20-50	11 (20.8%)	13 (24.5%)	24 (22.6%)
50-100	18 (34.0%)	13 (24.5%)	31 (29.2%)
>100	13 (24.5%)	18 (34.0%)	31 (29.2%)
Baseline urticarial, eczematous or erythematous plaques count, n (%)			
0	6 (11.3%)	4 (7.5%)	10 (9.4%)
1-2	0	1 (1.9%)	1 (0.9%)
3-5	1 (1.9%)	1 (1.9%)	2 (1.9%)
6-10	2 (3.8%)	3 (5.7%)	5 (4.7%)
10-20	5 (9.4%)	8 (15.1%)	13 (12.3%)
20-50	14 (26.4%)	14 (26.4%)	28 (26.4%)
50-100	12 (22.6%)	9 (17.0%)	21 (19.8%)
>100	13 (24.5%)	13 (24.5%)	26 (24.5%)
Baseline Karnofsky performance status scale score			
n	53	53	106
Mean (SD)	79.4 (16.10)	83.4 (12.70)	81.4 (14.57)
Median	80.0	80.0	80.0
Q1 : Q3	70.0 : 90.0	80.0 : 90.0	70.0 : 90.0
Min : Max	50 : 100	60 : 100	50 : 100
Baseline eosinophils (10^9/L)			
n	53	53	106
Mean (SD)	0.9430 (1.16090)	1.1046 (1.48220)	1.0238 (1.32741)
Median	0.4800	0.6500	0.5000
Q1 : Q3	0.2300 : 0.9600	0.3200 : 1.0300	0.2600 : 1.0300

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Min : Max	0.015 : 5.100	0.015 : 6.320	0.015 : 6.320
Baseline total IgE (kU/L)			
n	51	53	104
Mean (SD)	1860.6 (3102.72)	1502.0 (3041.51)	1677.8 (3062.02)
Median	580.0	424.0	510.0
Q1 : Q3	204.0 : 2511.0	157.0 : 1060.0	169.0 : 1486.0
Min : Max	15 : 18220	2 : 15070	2 : 18220
Baseline BP180 IgG (U/mL)			
n	40	41	81
Mean (SD)	320.6 (1004.32)	153.5 (310.81)	236.0 (739.65)
Median	61.5	72.0	64.0
Q1 : Q3	17.0 : 99.5	35.0 : 99.0	23.0 : 99.0
Min : Max	2 : 6200	1 : 1460	1 : 6200
Baseline BP230 IgG (U/mL)			
n	40	41	81
Mean (SD)	40.1 (36.38)	82.4 (207.32)	61.5 (150.30)
Median	33.0	6.0	14.0
Q1 : Q3	4.5 : 72.0	2.0 : 65.0	3.0 : 69.0
Min : Max	1 : 110	0 : 1050	0 : 1050

Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.1.2.2

[1] The categorization as new onset or relapsed active disease was done by the investigators based on their clinical judgement where participants with BP whose current active disease was due to a relapse at the time of screening were categorized as "relapsed active disease" and those without relapsed active disease were categorized as "new onset disease".

Medical History and Concurrent Illnesses

The medical history and concurrent illnesses reported among participants in this study were consistent with those typically seen in elderly individuals and patients with BP.

As expected among elderly participants with BP, there was a high frequency of medical history findings in the SOCs of Skin and subcutaneous tissue disorders, Vascular disorders, Metabolism and nutrition disorders, Nervous system disorders, Infections and infestations, and Cardiac disorders. Additionally, Musculoskeletal and connective tissue disorders and Surgical and medical procedures were also reported in a high proportion of participants, as expected in a population of elderly individuals.

Please also refer to Clinical Safety Section for more detailed information.

Prior and concomitant medications

Prior Medications for BP

Overall, 94.3% (100/106) of participants had used at least 1 prior medication for BP. Prior medication use for BP was generally balanced across the treatment groups. The most frequently reported prior medications for BP by therapeutic class were topical corticosteroids, corticosteroids for systemic use, antihistamines for systemic use and antibacterials for systemic use.

Table 10. Prior Medications for BP by Therapeutic Class (Reported in ≥5% of the Total Population; FAS)

ATC Level 2	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants with at least one prior medication for bullous pemphigoid	51 (96.2%)	49 (92.5%)	100 (94.3%)
Corticosteroids, dermatological preparations	39 (73.6%)	40 (75.5%)	79 (74.5%)
Corticosteroids for systemic use	34 (64.2%)	33 (62.3%)	67 (63.2%)
Antihistamines for systemic use	18 (34.0%)	20 (37.7%)	38 (35.8%)
Antibacterials for systemic use [1]	13 (24.5%)	11 (20.8%)	24 (22.6%)
Immunosuppressants [2]	6 (11.3%)	13 (24.5%)	19 (17.9%)
Emollients and protectives	7 (13.2%)	8 (15.1%)	15 (14.2%)
Analgesics	3 (5.7%)	6 (11.3%)	9 (8.5%)
Antipruritic, incl. antihistamines, anesthetics, etc.	2 (3.8%)	7 (13.2%)	9 (8.5%)
Antibiotics and chemotherapeutics for dermatological use	1 (1.9%)	7 (13.2%)	8 (7.5%)
Antimycotics for systemic use [3]	4 (7.5%)	4 (7.5%)	8 (7.5%)
Drugs for acid related disorders	2 (3.8%)	5 (9.4%)	7 (6.6%)
Psycholeptics	2 (3.8%)	5 (9.4%)	7 (6.6%)

WHODrug-Global-B3 dictionary applied.
A participant for whom 2 or more medications with different standardized medication names within the same ATC level have been reported is counted only once for that ATC level.
The table is sorted by descending order of frequency of ATC level 2 in the total group.
[1] Includes tetracycline class of antibiotics used for BP (eg, doxycycline)
[2] Includes systemic immunosuppressants or biologics (eg, methotrexate, mycophenolate mofetil, azathioprine, tofacitinib)
[3] Includes dapsone
Abbreviations: ATC=Anatomical Therapeutic Chemical; BP=bullous pemphigoid; FAS=full analysis set; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.1.3.2

Concomitant Medications for BP (Including Background OCS, Rescue, and Prohibited Medications)

Per the protocol, all participants, regardless of treatment assignment, were to receive a background standard regimen of OCS to achieve control of disease activity.

The other most frequently used concomitant medications for BP (including those used as rescue medications and prohibited medications) during the 52-week treatment period up to data cutoff by therapeutic class were:

- Corticosteroids, dermatological preparations (placebo: 58.5% [31/53]; dupilumab 300 mg Q2W: 43.4% [23/53]).
- Antihistamines for systemic use (placebo: 17.0% [9/53]; dupilumab 300 mg Q2W: 28.3% [15/53]).

Note: A higher proportion of participants in the placebo group initiated, discontinued, or changed dosage regimen of systemic antihistamines after baseline (ie. prohibited medication; placebo: 15.1% [8/53]; dupilumab: 3.8% [2/53]).

Numbers analysed

All efficacy endpoints were evaluated on the FAS, which was considered the primary analysis set.

The FAS was defined as all randomized participants (n=106) analyzed according to the treatment group allocated by randomization (ie, as randomized) regardless of whether the treatment kit was used or not.

Outcomes and estimation

Week 36
A summary of results for the primary and secondary endpoints at Week 36 is provided below.

Table 11. Primary and Secondary Efficacy Endpoint Results for the Prespecified Statistical Hierarchy (FAS)

Endpoint at Week 36 (Presented in Hierarchical Testing Order)	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value
Primary Endpoint			
1. Proportion of Participants Achieving Sustained Remission at Week 36	18.3%	6.1%	12.2% (-0.79%, 26.10%) ***p = 0.0645***
Key Secondary Endpoints			
2. Percent Change in BPDAI Activity Score from Baseline to Week 36, LS Mean % Change (SE)	-76.7 (6.89)	-50.5 (7.04)	-26.2 (-42.83, -9.50) p = 0.0021
3. Time to First Use of Rescue Medication (Days) up to Week 36, Restricted Mean Event Time (SE), HR	168.9 (10.96)	126.8 (8.17)	0.48 (0.300, 0.770) p = 0.0023
4. Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36	39.8%	10.5%	29.3% (12.79%, 45.04%) p = 0.0006
5. Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36, LS Mean % Change (SE)	-51.8 (6.66)	-26.7 (6.59)	-25.2 (-41.47, -8.85) p = 0.0025
6. Total Cumulative Dose of OCS (mg) from Baseline to Week 36, LS Mean (SE)	4184.93 (454.733)	5121.15 (473.034)	-936.21 (-2085.387, 212.961) p = 0.1092
Other Secondary Endpoints in the Statistical Testing Hierarchy			
7. Duration of Complete Remission (Days) While Not Requiring OCS up to Week 36, LS Mean (SE)	38.7 (7.88)	12.9 (8.08)	25.7 (5.85, 45.63) p = 0.0112
8. Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36	38.6%	9.8%	28.8% (12.79%, 44.06%) p = 0.0006
9. Change from Baseline to Week 36 in Percent BSA of BP Involvement, LS Mean Change (SE)	-24.07 (2.411)	-17.51 (2.544)	-6.57 (-12.659, -0.478) p = 0.0345
10. Change in BP180 Autoantibody IgG Titers from Baseline to Week 36, LS Mean Change (SE)	-162.80 (26.497)	-155.26 (26.745)	-7.54 (-67.140, 52.059) p = 0.8042
11. Change in ABQOL from Baseline to Week 36, LS Mean Change (SE)	-7.09 (1.458)	-3.41 (1.492)	-3.68 (-7.320, -0.039) p = 0.0476

Note: The hierarchical testing procedure broke at position 1 for the primary endpoint. P-values that are multiplicity-controlled are bolded. P-values for all secondary endpoints after the hierarchy break are nominal values.

Week 52

A summary of results for the secondary endpoints at Week 52 is provided below.

Table 12. Primary and Secondary Efficacy Endpoint Results for the Prespecified Statistical Hierarchy (FAS)

Secondary Endpoint at Week 52	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) Nominal P-value
Proportion of Participants Achieving Sustained Remission at Week 52	14.2%	6.1%	8.2% (-4.21%, 21.40%) p = 0.2089
Percent Change in BPDAI Activity Score from Baseline to Week 52, LS Mean % Change (SE)	-76.1 (6.85)	-49.1 (7.02)	-27.0 (-43.54, -10.37) p = 0.0014
Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 52	36.4%	8.3%	28.1% (12.44%, 43.55%) p = 0.0006
Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 52, LS Mean % Change (SE)	-53.0 (6.44)	-23.4 (6.41)	-29.5 (-45.23, -13.80) p = 0.0002
Total Cumulative Dose of OCS (mg) from Baseline to Week 52, LS Mean (SE)	5133.03 (788.414)	7159.09 (820.144)	-2026.06 (-4018.490, -33.624) p = 0.0463
Duration of Complete Remission (Days) While Not Requiring OCS up to Week 52, LS Mean (SE)	67.2 (14.13)	24.7 (15.11)	42.5 (6.77, 78.24) p = 0.0198
Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 52	34.4%	9.9%	24.5% (8.89%, 39.75%) p = 0.0024
Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 75% from Baseline to Week 52	36.6%	10.6%	26.0% (10.05%, 41.40%) p =0.0016
Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 50% from Baseline to Week 52	37.2%	11.2%	25.9% (9.86%, 41.36%) p = 0.0019
Change from Baseline to Week 52 in Percent BSA of BP Involvement, LS Mean Change (SE)	-23.89 (2.445)	-16.59 (2.588)	-7.30 (-13.470, -1.122) p = 0.0206
Change in BP180 Autoantibody IgG Titers from Baseline to Week 52, LS Mean Change (SE)	-137.60 (53.315)	-133.02 (57.248)	-4.58 (-139.885, 130.728) p = 0.9471
Change in BP230 Autoantibody IgG Titers from Baseline to Week 52, LS Mean Change (SE)	-18.83 (27.802)	-33.33 (29.392)	14.49 (-56.142, 85.130) p = 0.6876
Change in ABQOL from Baseline to Week 52, LS Mean Change (SE)	-7.29 (1.465)	-3.27 (1.508)	-4.02 (-7.680, -0.365) p = 0.0311
Proportion of participants who do not achieve control of disease activity (up to week 52), n (%)	1 (1.9)	4 (7.5)	-5.7 (-16.31, 3.34) p = 0.2414
Proportion of participants who relapse after achieving control of disease activity (up to week 52), n (%)	40 (76.9)	45 (91.8)	-14.9 (-29.39, -0.65) p = 0.0461
Proportion of participants who do not achieve complete remission (up to week 52), n (%)	18 (34.0)	27 (50.9)	-17.0 (-34.74, 1.93) p = 0.0843

Note: All P-values for week 52 endpoints are nominal.

Primary efficacy endpoint

Proportion of Participants Achieving Sustained Remission at Week 36

The proportion of participants achieving sustained remission at week 36 was numerically higher in the dupilumab 300 mg Q2W group (18.2%) than in the placebo group (6.1%) with a difference of 12.2% (p=0.0645).

Table 13. Primary Analysis of the Proportion of Participants Achieving Sustained Remission at Week 36 (FAS)

Treatment	Number of Participants with Observed Data [1]	Number of Participants with Observed Sustained Remission at Week 36	Estimated Proportion (%)*	Difference (%) (95% CI) [2]	P-value [3]
Dupilumab 300 mg Q2W (N=53)	50	9	18.3	12.2 (-0.79, 26.10)	**0.0645****
Placebo (N=53)	51	3	6.1		

***Intercurrent Event and Missing Data Handling: Participants were considered non-responders after rescue treatment use. Participants with missing assessment of sustained remission at week 36 caused by discontinuation from the study before week 36 due to lack of efficacy, treatment-related AE, or death were considered non-responders. Participants with missing assessment of sustained remission at week 36 due to other reasons were imputed using multiple imputation.**
Participants were considered responders if they met the following 3 criteria: (1) achievement of complete remission and off OCS no later than week 16 after randomization; (2) absence of disease relapse from the time the participant completed the OCS taper to week 36; (3) absence of need for rescue therapy during the 36-week double-blind treatment period. Participants were considered non-responders if they met either of the following 2 criteria: (1) required doses greater than 0.75 mg/kg/day of prednisone (or prednisolone) and did not achieve control of disease activity by week 4; (2) experienced a loss of control of disease activity during the OCS taper period.
**= multiplicity-controlled p-value
[1] Participants with observed data consists of participants with observed responder status, observed non-responder status, or assigned non-responder status due to rescue treatment use or discontinuation from the study due to lack of efficacy, treatment-related AE, or death.

Analyses of the Components of the Primary Endpoint

A prespecified analysis of each component of the primary endpoint was performed using the same strategy and data handling methods as the primary analysis of the primary endpoint.

Table 14. Summary of Analyses of Each Component of the Primary Endpoint (FAS)

Endpoint Component(s)	Treatment	Proportion of Responders (%)	Treatment Difference (%) (95% CI) [3]	P-value [4]
Primary Analysis				
Proportion of Participants Achieving Sustained Remission at Week 36 [1]	Dupilumab 300 mg Q2W (N=53) Placebo (N=53)	18.3 4.0	12.2 (-0.79, 26.10)	0.0645**
Analyses of Each Component of the Primary Endpoint				

Endpoint Component(s)	Treatment	Proportion of Responders (%)	Treatment Difference (%) (95% CI) [3]	P-value [4]
Participants with Absence of Disease Relapse from Completion of OCS Taper to Week 36 [5]	Dupilumab 300 mg Q2W (N=31) Placebo (N=20)	47.6 20.0	32.7 (5.34, 54.54)	0.0416^^
Participants with Absence of Rescue Treatment During the 36-week Treatment Period	Dupilumab 300 mg Q2W (N=53) Placebo (N=53)	40.1 11.8	28.2 (11.66,43.90)	0.0009^^
Participants Achieving Complete Remission and Off OCS No Later than Week 16 After Randomization	Dupilumab 300 mg Q2W (N=53) Placebo (N=53)	34.6 26.6	8.0 (-9.75, 25.35)	0.5283^^

Intercurrent Event and Missing Data Handling: Analysis of each component of the primary endpoint was performed using the same strategy and data handling method as the primary analysis.
**=multiplicity-controlled p-value.
^^= Statistical testing performed outside hierarchy; therefore the p-value is considered nominal.
[1] Participants were considered responders if they met the following 3 criteria: (i) achievement of complete remission and off OCS no later than week 16 after randomization; (ii) absence of disease relapse from the time the participant completed the OCS taper to week 36; (iii) absence of need for rescue therapy during the 36-week double-blind treatment period. Participants were considered non-responders if they met either of the following 2 criteria: (i) required doses greater than 0.75 mg/kg/day of prednisone (or prednisolone) and did not achieve control of disease activity by week 4; (ii) experienced a loss of control of disease activity during the OCS taper period.

Secondary efficacy endpoints

Proportion of Participants Achieving Sustained Remission at Week 52

The proportion of participants achieving sustained remission at week 52 was numerically higher in the dupilumab 300 mg Q2W group than in the placebo group (14.3% vs 6.1%; nominal p=0.2089). Of the 9 participants in the dupilumab group with observed sustained remission at week 36, 7 participants maintained sustained remission at week 52. Of the 2 dupilumab-treated participants who did not maintain sustained remission, 1 participant experienced a relapse between weeks 36 and 52. The other participant received treatment with commercially-available dupilumab at the week 52 and was thus categorized as having received a rescue medication. All three participants who achieved sustained remission in the placebo group at week 36 maintained sustained remission at week 52.

Proportion of Participants who Relapse after Achieving Control of Disease Activity up to Week 36 and Week 52

Up to week 36, 73.1% (38/52) of participants in the dupilumab group experienced a disease relapse after achieving initial control of disease as compared to 91.8% (45/49) in the placebo group treatment difference -18.8%; nominal p=0.0165).

Up to week 52, 76.9% (40/52) of participants in the dupilumab group experienced a disease relapse after achieving initial control of disease as compared to 91.8% (45/49) in the placebo group treatment difference versus placebo -14.9%; nominal p=0.0461).

Time to First Use of Rescue Medication (up to Week 36)

The restricted mean time to the first use of a rescue medication was longer in the dupilumab 300 mg Q2W group (168.9 days) compared with the placebo group (126.8 days) and there was a statistically significant 52% lower risk of rescue medication use in participants in the dupilumab 300 mg Q2W group compared with placebo (HR 0.48; p=0.0023).

Table 15. Primary Analysis of Time to First Use of Rescue Medication (Days) up to Week 36 (FAS)

Treatment	Number of Participants with Events (Censored)*	Restricted Mean Event Time (SE) [1]	Median Event Time (95% CI) [1]	Hazard Ratio (95% CI) [2]	P-value [2]
Dupilumab 300 mg Q2W (N=53)	31 (22)	168.9 (11.03)	124.0 (114.00, NE)	0.48 (0.300, 0.770)	0.0023**
Placebo (N=53)	46 (7)	126.8 (8.17)	113.5 (110.00, 115.00)		

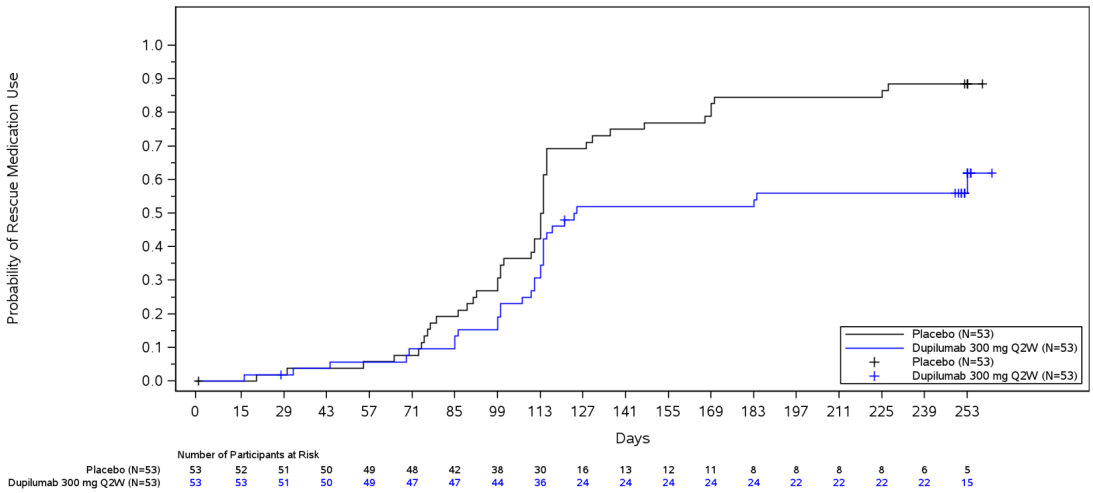
***Intercurrent Event and Missing Data Handling: Participants were considered to have used recue treatment at the time of discontinuation from the study due to lack of efficacy, treatment-related AE, or death. Participants were censored at the time of discontinuation from the study due to other reasons**.
**=multiplicity-controlled p-value

[1] Restricted mean event time and corresponding SE and median event time and corresponding CI are based on the Kaplan-Meier method. The restricted mean event time was calculated up to study day 253 (ie, week 36).

[2] Hazard ratio, CI, and p-value are based on a cox proportional hazards model including treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/ immunosuppressant use (Yes versus No) as covariates.
Abbreviations: AE=adverse event; BP=bullous pemphigoid; CI=confidence interval; FAS=full analysis set; NE=not estimable; OCS=oral corticosteroids; Q2W=every 2 weeks; SE=standard error.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.5r

The Figure 12 below displays time to the first use of a rescue medication (days) up to week 36. The 2 curves start to separate between days 71 and 85 (approximately weeks 10 and 12) as the OCS was being tapered.

Figure 12. Kaplan-Meier Curve: Time to First Use of Rescue Medication (Days) up to Week 36 (FAS)



Intercurrent Event and Missing Data Handling: Participants were considered to have used recue treatment at the time of discontinuation from the study due to lack of efficacy,- treatment-related AE,- or death. Participants were censored at the time of discontinuation from the study due to other reasons.

Abbreviations: AE=adverse event; FAS=full analysis set; OCS=oral corticosteroids; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTF 14.2.2.4

Rescue Medication for BP

A lower proportion of participants in the dupilumab 300 mg Q2W group (52.8% [28/53]) versus the placebo group (79.2% [42/53]) used a rescue medication up to week 36. Specific rescue medications used are listed below.

Table 16. Rescue Medications During the 36-week Treatment Period (FAS)

ATC Level 2 ATC Level 4 Standardized Medication Name	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants with at least one rescue medication during the first 36 weeks of the treatment period	42 (79.2%)	29 (54.7%)	71 (67.0%)
Corticosteroids for systemic use	39 (73.6%)	26 (49.1%)	65 (61.3%)
Glucocorticoids	39 (73.6%)	26 (49.1%)	65 (61.3%)
Prednisolone	19 (35.8%)	15 (28.3%)	34 (32.1%)
Prednisone	22 (41.5%)	10 (18.9%)	32 (30.2%)
Hydrocortisone	0	1 (1.9%)	1 (0.9%)
Corticosteroids, dermatological preparations	20 (37.7%)	14 (26.4%)	34 (32.1%)
Corticosteroids, very potent (group IV)	20 (37.7%)	14 (26.4%)	34 (32.1%)
Clobetasol propionate	14 (26.4%)	11 (20.8%)	25 (23.6%)
Clobetasol	6 (11.3%)	3 (5.7%)	9 (8.5%)
Immunosuppressants	5 (9.4%)	4 (7.5%)	9 (8.5%)
Other immunosuppressants	4 (7.5%)	1 (1.9%)	5 (4.7%)
Methotrexate	3 (5.7%)	0	3 (2.8%)
Azathioprine	1 (1.9%)	1 (1.9%)	2 (1.9%)
Selective immunosuppressants	1 (1.9%)	4 (7.5%)	5 (4.7%)
Mycophenolate mofetil	1 (1.9%)	4 (7.5%)	5 (4.7%)
Antineoplastic agents	0	2 (3.8%)	2 (1.9%)
CD20 (clusters of differentiation 20) inhibitors	0	2 (3.8%)	2 (1.9%)
Rituximab	0	2 (3.8%)	2 (1.9%)
Antipruritics, incl. antihistamines, anesthetics, etc.	2 (3.8%)	0	2 (1.9%)
Other antipruritics	2 (3.8%)	0	2 (1.9%)
Omalizumab	2 (3.8%)	0	2 (1.9%)
Other dermatological preparations	2 (3.8%)	0	2 (1.9%)
Agents for dermatitis, excluding corticosteroids	2 (3.8%)	0	2 (1.9%)
Dupilumab[1]	2 (3.8%)	0	2 (1.9%)

WHODrug-Global-B3 dictionary applied.
A participant for whom 2 or more medications with the same standardized medication name have been reported is counted only once for that term.
A participant for whom 2 or more medications with different standardized medication names within the same ATC level have been reported is counted only once for that ATC level.
[1] These cases were use of commercial dupilumab as rescue treatment after early discontinuation of study drug due to lack efficacy.
Abbreviations: ATC=Anatomical Therapeutic Chemical; FAS=full analysis set; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.1.3.7.a.r

Rescue Medication Used During the 52-week Treatment Period

The proportion of participants who used at least 1 rescue medication during the 52-week treatment period was lower in the dupilumab 300 mg Q2W group (56.6% [30/53]) than the placebo group

(81.1% [43/53]). There was 1 participant in each treatment group who had their first rescue medication use between weeks 36 to 52 (had not used any rescue medications prior to week 36).

Total Cumulative Dose of OCS from Baseline to Week 36 (imputation after non-OCS therapy)

The LS mean total cumulative dose of OCS from baseline to week 36 was lower in the dupilumab 300 mg Q2W group (4184.93 mg) than in the placebo group (5121.15 mg). The LS mean difference between the treatment groups favoring dupilumab was not statistically significant, showing a -936.21 mg difference (p=0.1092). Hence, the prespecified statistical hierarchical testing broke at this endpoint (see Table 17).

Sensitivity analyses for different strategies for imputing the OCS dose on days after non-OCS systemic rescue treatment also show lower mean total cumulative OCS doses.

Table 17. Primary Analysis of Total Cumulative Dose of OCS (mg) from Baseline to Week 36 (FAS)

Treatment	LS Mean (SE) [1]	LS Mean 95% CI [1]	LS Mean Difference vs. Placebo (95% CI) [1]	P-value [1]
Dupilumab 300 mg Q2W (N=53)	4184.93 (454.733)	(3282.643, 5087.221)	-936.21 (-2085.387, 212.961)	0.1092**
Placebo (N=53)	5121.15 (473.034)	(4182.544, 6059.747)		

Intercurrent Event and Missing Data Handling: Days after non-OCS systemic rescue treatment use were imputed by the WOCF method (ie, the highest daily OCS dose prior to any non-OCS systemic rescue treatment use). Missing data after study discontinuation were imputed with the average daily OCS dose among week 36 completers in each treatment group.
**= multiplicity-controlled p-value.
[1] LS means and differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline measurement included in the model as covariates.
Abbreviations: ANCOVA=analysis of covariance; BP=bullous pemphigoid; CI=confidence interval; FAS=full analysis set; LS=least squares; OCS=oral corticosteroids; Q2W=every 2 weeks; WOCF=worst observation carried forward.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.1r

Table 18. Summary of Sensitivity Analyses for the Total Cumulative Dose of OCS (mg) from Baseline to Week 36 (FAS)

Analysis Approach	Treatment	LS Mean (SE) (95% CI)	LS Mean 95% CI	LS Mean Difference vs. Placebo (95% CI)	P-value
Sensitivity Analysis					
If a participant had non-OCS systemic rescue treatment, days after non-OCS systemic rescue treatment use were excluded from the calculation of the total cumulative dose of OCS. Missing data after study discontinuation were imputed with the average daily OCS dose among week 36 completers in each treatment group	Dupilumab 300 mg Q2W (N=53)	3859.09 (312.004)	(3240.004, 4478.172)	-659.45 (-1447.925, 129.032)	0.1002^^
	Placebo (N=53)	4518.53 (324.561)	(3874.536, 5162.534)		
Observed OCS dose data after non-OCS systemic rescue treatment use were included in the calculation of the total	Dupilumab 300 mg Q2W (N=53)	3385.91 (173.800)	(3041.053, 3730.765)	-795.63 (-1234.844, -356.412)	0.0005^^

Analysis Approach	Treatment	LS Mean (SE) (95% CI)	LS Mean 95% CI	LS Mean Difference vs. Placebo (95% CI)	P-value
cumulative dose of OCS. Missing data after study discontinuation were imputed with the average daily OCS dose among week 36 completers in each treatment group	Placebo (N=53)	4181.54 (180.794)	(3822.802, 4540.272)		
Days after non-OCS systemic rescue treatment use and after discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method (ie, the highest daily OCS dose prior to any non-OCS systemic rescue treatment use). Missing data after discontinuation from the study due to other reasons were imputed with the average daily OCS dose among week 36 completers in each treatment group	Dupilumab 300 mg Q2W (N=53)	4478.98 (500.410)	(3486.059, 5471.901)	-1242.76 (-2507.368, 21.843)	0.0540^^
	Placebo (N=53)	5721.74 (520.549)	(4688.861, 6754.624)		

Note: All participants in both treatment groups were started on OCS at randomization with taper beginning by week 6 with the objective to taper off by week 16.
^^= Statistical testing performed outside hierarchy; therefore the p-value is considered nominal.
Abbreviations: AE=adverse event; ANCOVA=analysis of covariance; BP=bullous pemphigoid; CI=confidence interval; FAS=full analysis set; LS=least squares; OCS=oral corticosteroids; Q2W=every 2 weeks; WOCF=worst observation carried forward.
Source: PTTs 14.2.2.1.r, 14.2.2.1.1.r, 14.2.2.1.2.r, and 14.2.2.1.3.r

Total Cumulative Dose of OCS from Baseline to Week 52 (imputation after non-OCS therapy)

The LS mean total cumulative dose of OCS from baseline to week 52 was also lower in the dupilumab 300 mg Q2W group than in the placebo group (5133.03 mg vs 7159.09 mg) showing a -2026.06 mg treatment difference versus placebo (nominal p=0.0463).

Total Cumlative Dose of OCS to Week 36 and Week 52 (regardless of non-OCS rescue therapy)

Results for the total cumulative observed OCS dose calculated based on a treatment policy strategy (ie. regardless of non-OCS rescue therapy) from baseline to week 36 and week 52 is shown below.

Table 19. Total Cumulative Dose of OCS (mg) from Baseline to Week 36 and Week 52 regardless of non-OCS therapy

Total Cumulative Dose of OCS (mg) from Baseline to Week 36				
Treatment	LS Mean (SE) [1]	LS Mean 95% CI [1]	LS Mean Difference vs. Placebo (95% CI) [1]	P-value [1]
Dupilumab 300 mg Q2W (N=53)	3385.91 (173.800)	(3041.053, 3730.765)	-795.63 (-1234.844, -356.412)	0.0005
Placebo (N=53)	4181.54 (180.794)	(3822.802, 4540.272)		
Total Cumulative Dose of OCS (mg) from Baseline to Week 52				

Dupilumab 300 mg Q2W (N=53)	3704.79 (250.272)	(3208.192, 4201.380)	-1186.46 (-1818.931, -553.986)	0.0003
Placebo (N=53)	4891.24 (260.344)	(4374.665, 5407.824)		
Observed OCS dose data after non-OCS systemic rescue treatment use were included in the calculation of the total cumulative dose of OCS. Missing data after study discontinuation were imputed with the average daily OCS dose among week 36/52 completers in each treatment group. [1] LS means and differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline measurement included in the model as covariates.				

Mean observed OCS average daily dose

A reduction of approximately 5 mg/day in the mean observed OCS average daily dose is present from week 16 to week 36 between dupilumab-treated and placebo-treated participants (4.0 mg versus 9.3 mg per day) and maintained to week 52 (3.7 mg versus 8.6 mg per day).

Table 20. Summary of Percentage Reduction of OCS Dose Between Week 16 and Week 36 and Week 52, All Observed Values (FAS)

	Treatment		Difference in Means (Dupilumab 300 mg Q2W minus Placebo)	Percentage Reduction of Dupilumab 300 mg Q2W vs Placebo [1]
	Dupilumab 300 mg Q2W (N=53)	Placebo (N=53)		
Mean Observed OCS Average Daily Dose (mg) from Week 16 to Week 36 (SD)	4.0 (6.06)	9.3 (8.45)	-5.3	57.0%
Mean Observed OCS Average Daily Dose (mg) from Week 16 to Week 52 (SD)	3.7 (5.88)	8.6 (8.53)	-4.9	57.0%
[1] Percentage reduction was calculated as [1-(mean observed OCS average daily dose from Week 16 to Week 36 in the dupilumab 300 mg Q2W group/mean observed OCS average daily dose from Week 16 to Week 36 in the placebo group)]*100.				

Source: Appendix 6: Table Q4.i.a.ema, Appendix 7: Table Q4.i.b.ema

Duration of Complete Remission While Not Requiring OCS (up to Week 52)

Complete remission was defined as absence of new lesions and epithelialization of old lesions. The LS mean duration of complete remission while not requiring OCS up to week 52 was longer in the dupilumab 300 mg Q2W group (67.2 days) than in the placebo group (24.7 days). The LS mean treatment difference was statistically significant (42.5 days; nominal p=0.0198).

Table 21, Primary Analysis of Duration of Complete Remission (Days) While Not Requiring OCS Up to Week 52 (FAS)

Treatment	LS Mean (SE) [1]	LS Mean 95% CI [1]	LS Mean Difference vs. Placebo (95% CI) [1]	P-value [1]
Dupilumab 300 mg Q2W (N=53)	67.2 (14.13)	(39.49, 94.88)	42.5 (6.77, 78.24)	0.0198**
Placebo (N=53)	24.7 (15.11)	(-4.93, 54.30)		

Treatment	LS Mean (SE) [1]	LS Mean 95% CI [1]	LS Mean Difference vs. Placebo (95% CI) [1]	P-value [1]

Intercurrent Event and Missing Data Handling: Participants were considered as not achieving complete remission after rescue treatment use. Participants with missing assessment of complete remission caused by discontinuation from the study before week 52 due to lack of efficacy, treatment-related AE, or death were considered as not achieving complete remission. Participants with missing assessment of complete remission due to other reasons were imputed using multiple imputation.

**=nominal p-value.

[1] LS means and differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), and prior corticosteroid/immunosuppressant use (Yes versus No) included in the model as covariates.

Abbreviations: ANCOVA=analysis of covariance; BP=bullous pemphigoid; CI=confidence interval; FAS=full analysis set; LS=least squares; OCS=oral corticosteroids; SE=standard error; Q2W=every 2 weeks.

Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.13.B

Percent Change in BPDAI Activity Score from Baseline to Week 36 and to Week 52

The LS mean percent change from baseline in the total BPDAI activity score at week 36 was greater in the dupilumab 300 mg Q2W group (-76.7%) than in the placebo group (-50.5%) (LS mean treatment difference -26.2%; p=0.0021).

Table 22. Primary Analysis of Percent Change in BPDAI Activity Score from Baseline to Week 36 (FAS)

Visit	Treatment	Baseline Mean (SD)	Mean % Change (SD)	Number of Participants with Observed Data [1]/ Imputed Data	LS Mean % Change (SE) [2]	LS Mean % Change 95% CI [2]	LS Mean Difference vs. Placebo (95% CI) [2]	P-value [2]
Week 36	Dupilumab 300 mg Q2W (N=53)	62.51 (31.580)	-78.5 (28.47)	50/3	-76.7 (6.89)	(-90.19, -63.18)	-26.2 (-42.88, -9.54)	0.0021**
	Placebo (N=53)	58.55 (28.469)	-51.1 (54.26)	52/1	-50.5 (7.04)	(-64.27, -36.68)		

Intercurrent Event and Missing Data Handling: Values after first rescue treatment were set to missing and were imputed with the worst value from the closest visit on or prior to rescue medication use and afterwards up to and including week 36. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
=multiplicity-controlled p-value.

[1] Note that participants with observed data includes participants with worst value imputation due to rescue treatment and participants with WOCF imputation due to missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death. Participants with imputed data consists of participants with imputed values for missing data due to other reasons.

[2] LS mean changes and differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes vs No), and baseline measurement included in the model as covariates.

Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.4

A numerically greater mean percent change (reduction) from baseline in BPDAI activity score was seen at week 36 in dupilumab 300 mg Q2W participants than placebo participants (LS mean percent change: -88.5% vs -73.6%, nominal p=0.0293; using treatment policy strategy for rescue medication use.

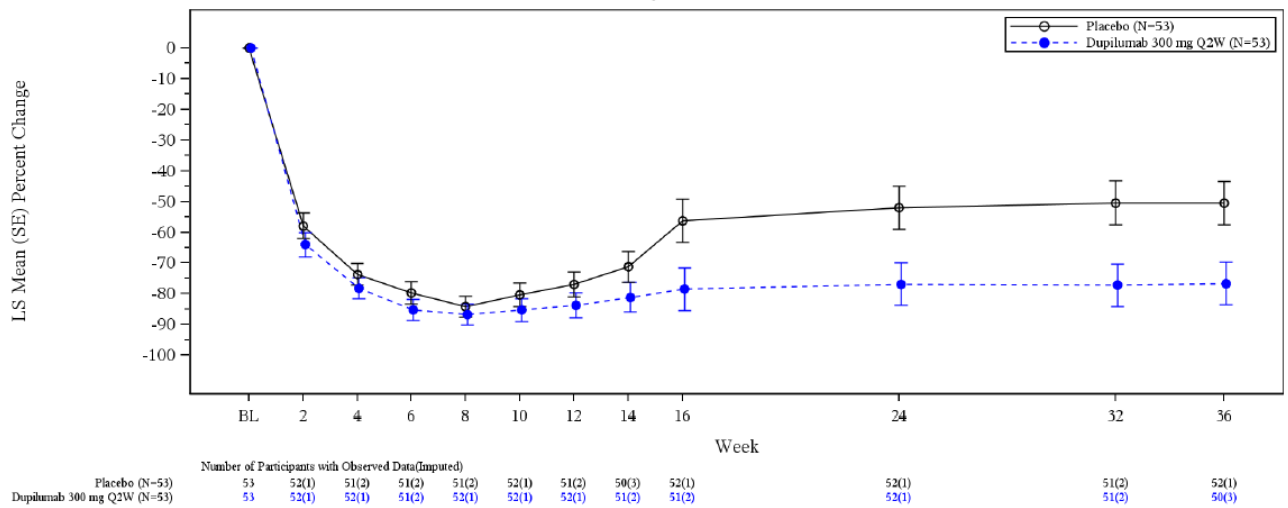
Table 23. Treatment Policy Analysis of Percent Change in BPDAI Activity Score from Baseline to Week 36 and to Week 52 (FAS)

	Week 36			Week 52		
	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value
Percent Change in BPDAI Activity Score from Baseline to Week 36/52, LS Mean % Change (SE) [8]	-88.5 (5.51) [9]	-73.6 (5.65) [9]	-14.9 (-28.36, -1.50) [9] p = 0.0293 [9]	-91.6 (5.08) [9]	-75.1 (5.18) [9]	-16.5 (-28.88, -4.17) [9] p = 0.0088 [9]

[8] Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
[9] LS means, mean changes, differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline measurement included in the model as covariates.

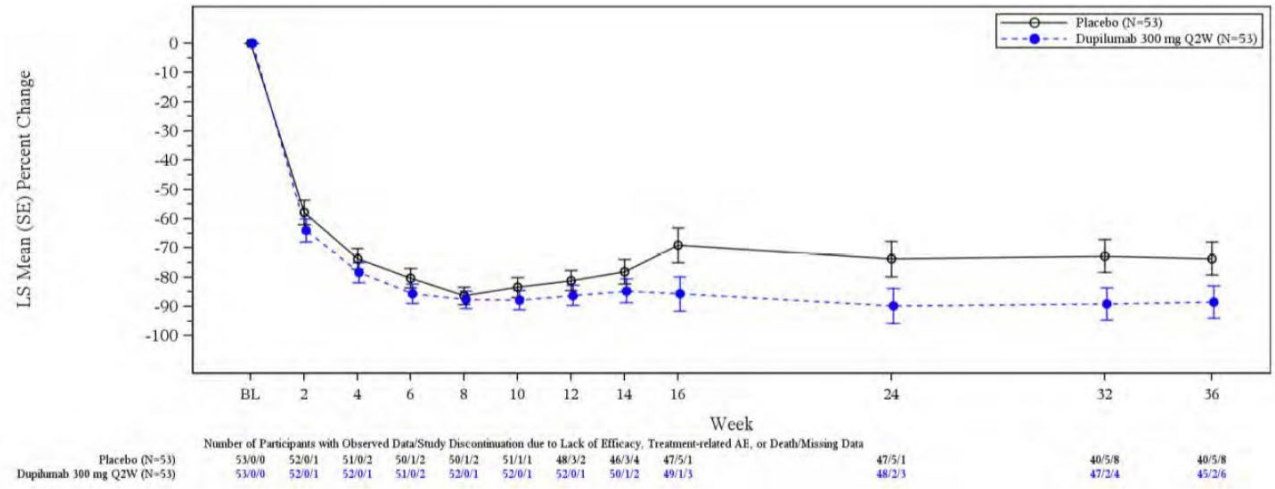
The percent change in BPDAI activity score over time from baseline to week 36 is shown below for the primary end the treatment policy analysis.

Figure 13. Line Chart: LS Mean (SE) Percent Change in BPDAI Activity Score from Baseline to Week 36 (FAS)



Intercurrent Event and Missing Data Handling: Values after first rescue treatment were set to missing and were imputed with the worst value from the closest visit on or prior to rescue medication use and afterwards up to and including week 36. Missing values caused by discontinuation from the study due to lack of efficacy,¬ treatment-related AE,¬ or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
Abbreviations: BPDAI=bullous pemphigoid disease area index; FAS=full analysis set; LS=least squares; Q2W=every 2 weeks; SE=standard error; WOCF=worst observation carried forward.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTF 14.2.2.3.r

Figure 14. Line Chart: LS Mean (SE) Percent Change in BPDAI Activity Score from Baseline to Week 36 (FAS) (regardless of rescue medication)



Treatment policy strategy was used for rescue medication use. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the worst observation carried forward method. Missing values due to other reasons were imputed by multiple imputation.
Source: Appendix 8 Figure Q7.iiii.b36.ema

Proportion of Participants Who Achieved a Reduction in BPDAI Activity Score of at Least 90%, 75%, and 50% From Baseline to Week 36 and to Week 52

A significantly greater proportion of participants achieved a reduction in BPDAI activity score of at least 90% (ie, almost complete disease clearance) from baseline to week 36 in the dupilumab 300 mg Q2W group compared with the placebo group (40.5% vs 9.8%, p=0.0003).

A dupilumab treatment benefit was also observed in the proportion of participants achieving a reduction in BPDAI activity score of least 50% and 75% from baseline to week 36 compared with placebo (42.9% vs 13.2%; nominal p=0.0006, and 40.7% vs 12.5%; nominal p=0.0012).

Table 24. Primary Analysis of Proportion of Participants Achieving a Reduction in BPDAI Activity Score of ≥90%, ≥75%, and ≥50% from Baseline to Week 36 (FAS)

BPDAI Activity Score Endpoint	Treatment	Number of Participants with Observed Data [1]	Number of Participants with Observed Specified Reduction in BPDAI Activity Score	Estimated Proportion (%)	Difference (%) (95% CI) [2]	P-value [3]
Reduction in BPDAI activity score of at least 90% from baseline to week 36	Dupilumab 300 mg Q2W	50	19	40.5	30.6 (14.53, 45.93)	0.0003 **
	Placebo	52	5	9.8		
Reduction in BPDAI activity score of at least 75% from baseline to week 36	Dupilumab 300 mg Q2W	50	19	40.7	28.2 (11.43, 43.98)	0.0012^^
	Placebo	52	6	12.5		
Reduction in BPDAI activity score of at least 50% from baseline to week 36	Dupilumab 300 mg Q2W	50	20	42.9	29.7 (12.90, 45.41)	0.0006^^
	Placebo	52	6	13.2		

Intercurrent Event and Missing Data Handling: Participants were considered non-responders after rescue treatment use. Participants with missing values caused by discontinuation from the study before week 36 due to lack of efficacy,¬ treatment-related AE,¬ or death were considered non-responders. Missing values due to other reasons were imputed using multiple imputation of the continuous data of the BPDAI activity score.

**=multiplicity-controlled p-value.
^^-Statistical testing performed outside hierarchy; therefore the p-value is considered nominal.
[1] Participants with observed data consists of participants with observed responder status,¬ observed non-responder status,¬ or assigned non-responder status due to rescue treatment use or discontinuation from the study due to lack of efficacy,¬ treatment-related AE,¬ or death.

[2] CI for the difference between dupilumab and placebo is based on the Miettinen and Nurminen method.
[3] P-value is based on Barnard's exact test.
Abbreviations: AE=adverse event; BPDAI=bullous pemphigoid disease area index; CI=confidence interval; FAS=full analysis set; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTTs 14.2.2.8.1.1, 14.2.2.8.2.1 and 14.2.2.8.3.1

Up to week 52, a numerically higher proportion of participants in the dupilumab group compared with the placebo group achieved a reduction in BPDAI activity score from baseline of at least 90% (34.4% vs 9.9%, nominal p=0.0024), 75% (36.6% vs 10.6%; nominal p=0.0016), and 50% (37.2% vs 11.2%; nominal p=0.0019).

A numerically greater proportion of participants treated with dupilumab versus placebo achieved almost complete control of the disease activity at week 36, which was maintained at week 52 regardless of rescue use (i.e., a reduction from baseline in BPDAI activity score of ≥90% at week 36: 75.0% vs 53.0%, nominal p=0.0194; using treatment policy for rescue medication use).

Table 25. Treatment policy analysis of Proportion of Participants Achieving a Reduction in BPDAI Activity Score of ≥90%, ≥75%, and ≥50% from Baseline to Week 36 and to Week 52 (FAS)

	Week 36			Week 52		
	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value
Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36/52	75.0% [13]	53.0% [13]	22.0% (3.16%, 39.52%) [3] p = 0.0194 [4]	79.8% [13]	55.4% [13]	24.4% (5.69%, 41.85%) [3] p = 0.0084 [4]

[3] CI for the difference between dupilumab and placebo is based on the Miettinen and Nurminen method.
[4] P-value is based on Barnard's exact test.
[13] Estimated proportion with imputation (Participants with missing values caused by discontinuation from the study before week 36/52 due to lack of efficacy, treatment-related AE, or death were considered non-responders. Missing values due to other reasons were imputed using multiple imputation).

Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36 and to Week 52

Significantly more dupilumab-treated participants (39.8%) demonstrated improvement (reduction) in the weekly average of daily peak pruritus NRS score ≥4 from baseline at week 36 than the placebo-treated participants (10.6%). The treatment difference was statistically significant (29.3%, p=0.0006).

Table 26. Primary Analysis of Proportion of Participants with Improvement of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36 (FAS)

Treatment	Number of Participants with Observed Data [1]	Number of Participants with Observed Improvement of Weekly Average of Daily Peak Pruritus NRS ≥4	Estimated Proportion (%)*	Difference (%) (95% CI) [2]	P-value [3]
Dupilumab 300 mg Q2W (N=53)	48	19	39.8	29.3 (12.76, 45.06)	0.0006**
Placebo (N=53)	51	5	10.6		

***Intercurrent Event and Missing Data Handling: Participants were considered non-responders after rescue treatment use. Participants with missing values caused by discontinuation from the study before week 36 due to lack of efficacy, treatment-related AE, or death were considered non-responders. Missing values due to other reasons were imputed using multiple imputation of the continuous data of the weekly average of daily peak pruritus NRS**.
**=multiplicity-controlled p-value.
[1] Participants with observed data consists of participants with observed responder status, observed non-responder status, or assigned non-responder status due to rescue treatment use or discontinuation from the study due to lack of efficacy, treatment-related AE, or death.
[2] CI for the difference between dupilumab and placebo is based on the Miettinen and Nurminen method.
[3] P-value is based on Barnard's exact test.
Abbreviations: AE=adverse event; CI=confidence interval; FAS=full analysis set; NRS=numerical rating scale; Q2W=every 2 weeks.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.3.1

At week 52, a higher proportion of dupilumab-treated participants demonstrated improvement (reduction) in the weekly average of daily peak pruritus NRS score of ≥4 from baseline than placebo-treated participants (36.4% vs 8.3%). The treatment difference versus placebo was 28.1% (nominal p=0.0006).

A numerically greater proportion of participants in the dupilumab 300 mg Q2W group achieved a reduction in weekly average of daily peak pruritus NRS score of ≥4 from baseline at week 36 compared with placebo (71.7% vs 54.1%, nominal p=0.0645; using treatment policy strategy for rescue medication use).

Table 27. Treatment policy analysis of Proportion of Participants with Improvement of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36 and to Week 52 (FAS)

	Week 36			Week 52		
	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value
Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36/52	71.7% [13]	54.1% [13]	17.5% (-1.62%, 35.62%) [3] p = 0.0645 [4]	77.5% [13]	53.5% [13]	24.0% (4.90%, 41.73%) [3] p = 0.0092 [4]

[3] CI for the difference between dupilumab and placebo is based on the Miettinen and Nurminen method.
[4] P-value is based on Barnard's exact test.
[13] Estimated proportion with imputation (Participants with missing values caused by discontinuation from the study before week 36/52 due to lack of efficacy, treatment-related AE, or death were considered non-responders. Missing values due to other reasons were imputed using multiple imputation).

Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36

The LS mean percent change from baseline in the weekly average of daily peak pruritus NRS at week 36 was greater in the dupilumab 300 mg Q2W group (-51.8%) than in the placebo group (26.7%) and the LS mean treatment difference was statistically significant (-25.2%; p=0.0025).

Table 28. Primary Analysis of Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36 (FAS)

Visit	Treatment	Baseline Mean (SD)	Mean % Change (SD)	Number of Participants with Observed Data [1]/ Imputed Data	LS Mean % Change (SE) [2]	LS Mean % Change 95% CI [2]	LS Mean Difference vs. Placebo (95% CI) [2]	P-value [2]
Week 36	Dupilumab 300 mg Q2W (N=53)	7.56 (1.644)	-51.4 (39.21)	48/3	-51.8 (6.66)	(-64.90, -38.78)	-25.2 (-41.47, -8.85)	0.0025**

Visit	Treatment	Baseline Mean (SD)	Mean % Change (SD)	Number of Participants with Observed Data [1]/ Imputed Data	LS Mean % Change (SE) [2]	LS Mean % Change 95% CI [2]	LS Mean Difference vs. Placebo (95% CI) [2]	P-value [2]
	Placebo (N=53)	7.42 (1.543)	-25.3 (38.92)	51/2	-26.7 (6.59)	(-39.59, -13.77)		

Intercurrent Event and Missing Data Handling: Values after first rescue treatment were set to missing and were imputed with the worst value from the closest visit on or prior to rescue medication use and afterwards up to and including week 36. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
**=multiplicity-controlled p-value.
[1] Note that participants with observed data includes participants with worst value imputation due to rescue treatment and participants with WOCF imputation due to missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death. Participants with imputed data consists of participants with imputed values for missing data due to other reasons.
[2] LS mean changes and differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline measurement included in the model as covariates.
Abbreviations: AE=adverse event; ANCOVA=analysis of covariance; BP=bullous pemphigoid; CI=confidence interval; FAS=full analysis set; LS=least squares; NRS=numerical rating scale; OCS=oral corticosteroids; Q2W=every 2 weeks; SD=standard deviation; SE=standard error; WOCF=worst observation carried forward.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.2.2.2.r

A numerically greater mean percent reduction from baseline in weekly average of the daily peak pruritus NRS score at week 36 in the dupilumab group compared with the placebo group, regardless of the higher rescue use in placebo-treated participants (LS mean percent change: -66.7% vs -51.4%, nominal p=0.0785; using treatment policy strategy for rescue medication use).

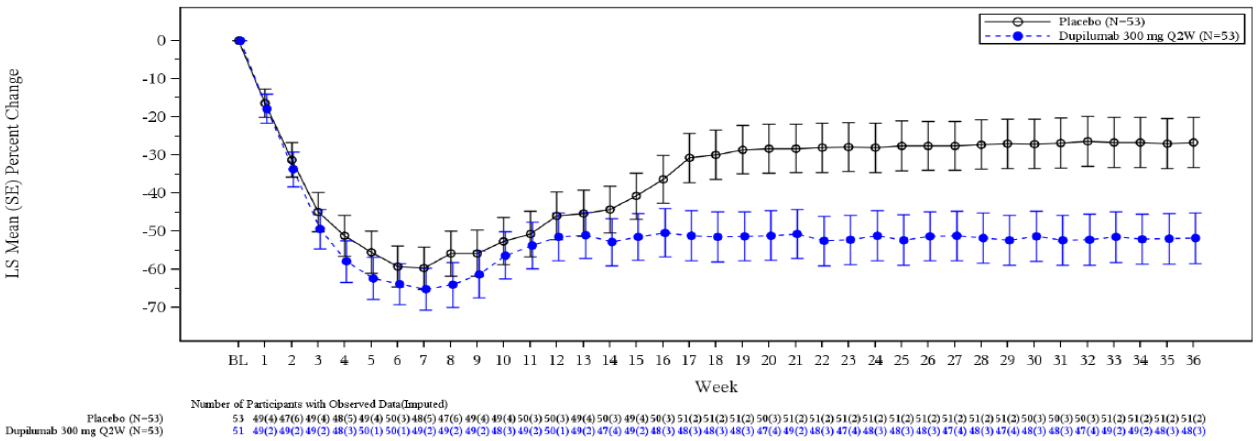
Table 29. Treatment policy analysis of Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36 and to Week 52 (FAS)

	Week 36			Week 52		
	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value	Dupilumab (N=53)	Placebo (N=53)	Treatment Difference (95% CI) P-value
Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36/52, LS Mean % Change (SE) [8]	-66.7 (6.96) [9]	-51.4 (6.87) [9]	-15.2 (-32.21, 1.74) [9] p = 0.0785 [9]	-75.6 (6.08) [9]	-48.6 (6.34) [9]	-27.0 (-42.21, -11.84) [9] p = 0.0005 [9]

[8] Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
[9] LS means, mean changes, differences, corresponding SEs and CIs, and p-values are based on an ANCOVA model with treatment group, baseline disease severity (moderate versus severe BP), region (North America versus Europe versus Asia), prior corticosteroid/immunosuppressant use (Yes versus No), and baseline measurement included in the model as covariates.

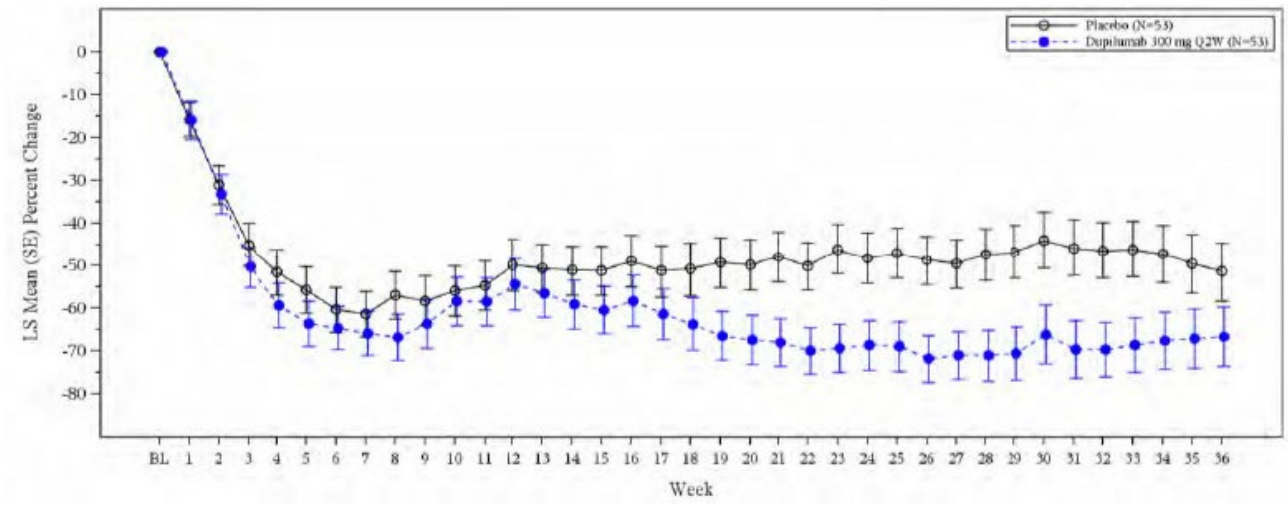
The figures below show the mean percent change in the weekly average of daily peak pruritus NRS score over time from baseline to week 36 for the primary and the treatment policy analysis.

Figure 15. Line Chart: LS Mean (SE) Percent Change in Weekly Average of Daily Peak Pruritus NRS Score from Baseline to Week 36 (FAS)



Intercurrent Event and Missing Data Handling: Values after first rescue treatment were set to missing and were imputed with the worst value from the closest visit on or prior to rescue medication use and afterwards up to and including week 36. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; NRS=numerical rating scale; Q2W=every 2 weeks; SE=standard error; WOCF=worst observation carried forward.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTF 14.2.2.2.r

Figure 16. Line Chart: LS Mean (SE) Percent Change in Weekly Average of Daily Peak Pruritus NRS Score from Baseline to Week 52 (FAS) (regardless of use of rescue medication)



Treatment policy strategy was used for rescue medication use. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the worst observation carried forward method. Missing values due to other reasons were imputed by multiple imputation.
Source: Appendix 8 Figure Q7.iiii.n36.ema

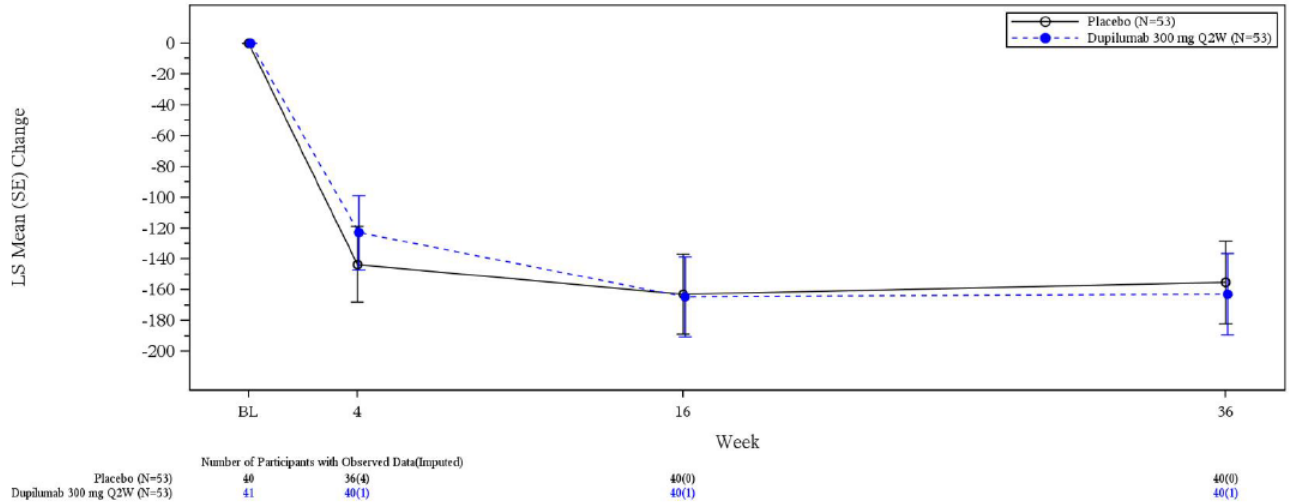
Secondary Biomarker Endpoints

Anti-BP180 IgG in Serum

The mean (SD) baseline concentration of BP180 IgG was 291.70 (841.915) U/mL in the dupilumab 300 mg Q2W group and 329.59 (913.355) U/mL in the placebo group. There were similar LS mean (SE) reductions from baseline in BP180 IgG autoantibody titers in both treatment groups at weeks 4, 16, and 36. At week 36, the LS mean (SE) change from baseline was -136.33 (53.247) U/mL in the dupilumab group and -137.57 (57.125) U/mL in the placebo group (p=0.9857). At week 52, the LS

mean (SE) change from baseline was (-137.60 [53.315] U/mL in the dupilumab 300 mg Q2W group and -133.02 [57.248] U/mL in the placebo (nominal p=0.9471).

Figure 17. Line Chart: LS Mean (SE) Change from Baseline in BP180 IgG Autoantibody Titer (U/mL) in Serum up to Week 36 (FAS)



Intercurrent Event and Missing Data Handling: Values after first rescue treatment were set to missing and were imputed with the worst value from the closest visit on or prior to rescue medication use and afterwards up to and including week 36. Missing values caused by discontinuation from the study due to lack of efficacy, treatment-related AE, or death were imputed by the WOCF method. Missing values due to other reasons were imputed by multiple imputation.
Note: All participants in both treatment groups were started on OCS at randomization with taper beginning by week 6 with the objective to taper off by week 16
Abbreviations: AE=adverse event; BL=baseline; FAS=full analysis set; IgG=immunoglobulin G; LS=least squares, N=number of participants; OCS=oral corticosteroids; Q2W=every 2 weeks; SE=standard error; WOCF=worst observation carried forward. Source: PTF 14.2.4.1.r

Anti-BP230 IgG in Serum

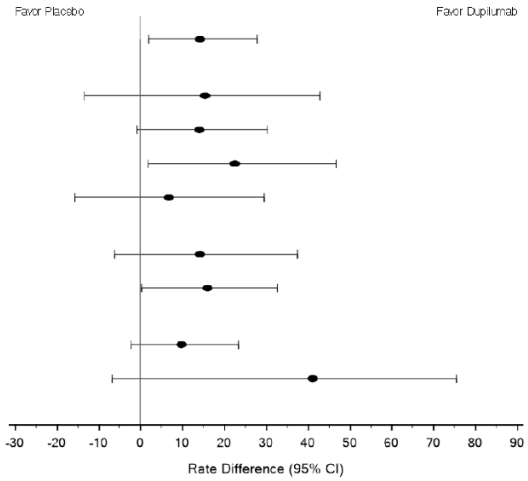
The mean (SD) baseline concentration of BP230 IgG in serum was 82.37 (207.320) U/mL in the dupilumab 300 mg Q2W group and 53.08 (86.847) U/mL in the placebo group. At week 36, the LS mean (SE) change from baseline was -18.49 (27.705) U/mL in the dupilumab group as compared with -33.91 (29.380) U/mL in the placebo group (nominal p=0.6680). The LS mean (SE) change from baseline at week 52 was -18.83 (27.802) U/mL in the dupilumab 300 mg Q2W group compared with -33.33 (29.392) U/mL in the placebo group (nominal p=0.6876).

Subgroup analysis

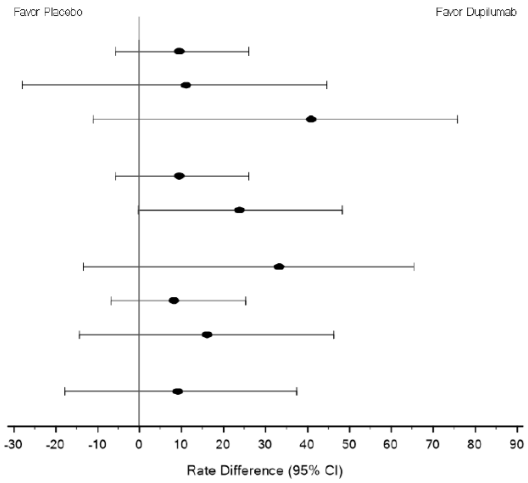
Analyses of the Primary Endpoint (Proportion of Participants Achieving Sustained Remission at Week 36) by Subgroups

Figure 18. Forest Plot: Proportion of Participants Achieving Sustained Remission at Week 36 by Subgroups

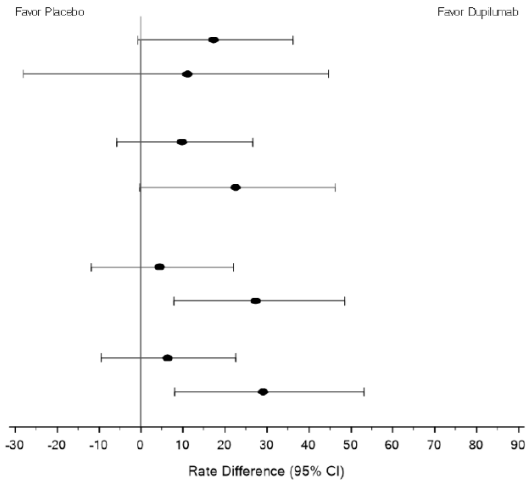
Subgroup	Placebo Rate	Dupilumab Rate	Rate Diff. (95% CI)
Overall			
Dupilumab 300 mg Q2W (N=53) vs Placebo (N=53)	4.0	18.2	14.2 (1.97, 27.74)
Age Group			
<65 years			
Dupilumab 300 mg Q2W (N=13) vs Placebo (N=11)	0.0	15.4	15.4 (-13.37, 42.86)
>=65 years			
Dupilumab 300 mg Q2W (N=40) vs Placebo (N=42)	5.0	19.1	14.1 (-0.79, 30.29)
>=65 to <75 years			
Dupilumab 300 mg Q2W (N=18) vs Placebo (N=20)	0.6	23.1	22.5 (1.84, 46.74)
>=75 years			
Dupilumab 300 mg Q2W (N=22) vs Placebo (N=22)	9.1	15.8	6.7 (-15.73, 29.48)
Sex			
Male			
Dupilumab 300 mg Q2W (N=21) vs Placebo (N=29)	7.2	21.3	14.2 (-6.24, 37.53)
Female			
Dupilumab 300 mg Q2W (N=32) vs Placebo (N=24)	0.2	16.1	16.0 (0.31, 32.66)
Ethnicity			
NOT HISPANIC OR LATINO			
Dupilumab 300 mg Q2W (N=43) vs Placebo (N=42)	2.5	12.2	9.8 (-2.22, 23.51)
NOT REPORTED			
Dupilumab 300 mg Q2W (N=8) vs Placebo (N=7)	1.1	42.3	41.1 (-6.85, 75.50)



Subgroup	Placebo Rate	Dupilumab Rate	Rate Diff. (95% CI)
Race			
WHITE			
Dupilumab 300 mg Q2W (N=35) vs Placebo (N=37)	5.5	15.0	9.5 (-5.63, 26.10)
ASIAN			
Dupilumab 300 mg Q2W (N=9) vs Placebo (N=7)	0.0	11.1	11.1 (-27.96, 44.65)
NOT REPORTED			
Dupilumab 300 mg Q2W (N=8) vs Placebo (N=6)	1.3	42.3	40.9 (-10.98, 75.70)
Race Group			
WHITE			
Dupilumab 300 mg Q2W (N=35) vs Placebo (N=37)	5.5	15.0	9.5 (-5.63, 26.10)
NON-WHITE			
Dupilumab 300 mg Q2W (N=18) vs Placebo (N=16)	0.5	24.3	23.8 (-0.21, 48.29)
Baseline Weight Group			
<60 kg			
Dupilumab 300 mg Q2W (N=9) vs Placebo (N=6)	0.0	33.3	33.3 (-13.37, 65.48)
>=60 to <90 kg			
Dupilumab 300 mg Q2W (N=31) vs Placebo (N=33)	3.2	11.4	8.3 (-6.78, 25.35)
>=90 kg			
Dupilumab 300 mg Q2W (N=13) vs Placebo (N=14)	7.7	23.8	16.1 (-14.24, 46.24)
Region			
North America			
Dupilumab 300 mg Q2W (N=12) vs Placebo (N=12)	0.0	9.2	9.2 (-17.81, 37.60)



Subgroup	Placebo Rate	Dupilumab Rate	Rate Diff. (95% CI)
Europe			
Dupilumab 300 mg Q2W (N=32) vs Placebo (N=34)	6.2	23.6	17.3 (-0.66, 36.33)
Asia			
Dupilumab 300 mg Q2W (N=9) vs Placebo (N=7)	0.0	11.1	11.1 (-27.96, 44.65)
Baseline Disease Severity			
Moderate (BPDAI activity score >=24 to <60)			
Dupilumab 300 mg Q2W (N=34) vs Placebo (N=36)	5.7	15.5	9.8 (-5.74, 26.77)
Severe (BPDAI activity score >=60)			
Dupilumab 300 mg Q2W (N=19) vs Placebo (N=17)	0.5	23.1	22.6 (-0.19, 46.27)
Prior Corticosteroid/Immunosuppressant Use			
Yes			
Dupilumab 300 mg Q2W (N=30) vs Placebo (N=32)	6.4	10.9	4.5 (-11.82, 21.96)
No			
Dupilumab 300 mg Q2W (N=23) vs Placebo (N=21)	0.4	27.7	27.4 (7.91, 48.73)
BP Status			
New onset			
Dupilumab 300 mg Q2W (N=35) vs Placebo (N=34)	6.2	12.5	6.3 (-9.45, 22.71)
Relapsed active disease			
Dupilumab 300 mg Q2W (N=18) vs Placebo (N=19)	0.1	29.2	29.1 (8.04, 53.18)



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for trial R668-BP-1902

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
Design	This study was a global, multicenter, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adults with BP		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 5 weeks Not applicable
Hypothesis	Superiority		
Treatment groups	Dupilumab 300 mg Q2W		Dupilumab 300 mg Q2W for 52 weeks, N = 53
	Matching placebo		Placebo Q2W for 52 weeks, N = 53
Endpoints and definitions	Primary endpoint	Sustained Remission at Week 36	Proportion of Participants Achieving Sustained Remission at Week 36
	Key Secondary endpoint	BPDAI Activity Score from Baseline to Week 36	Percent Change in BPDAI Activity Score from Baseline to Week 36
		Time to use of Rescue Medication (Days) up to Week 36	Time to First Use of Rescue Medication (Days) up to Week 36
		Improvement in Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36	Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36
		Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36	Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
		Total Cumulative Dose of OCS (mg) from Baseline to Week 36	Total Cumulative Dose of OCS (mg) from Baseline to Week 36
	Secondary endpoint	Complete Remission (Days) While Not Requiring OCS up to Week 36	Duration of Complete Remission (Days) While Not Requiring OCS up to Week 36
		Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36	Proportion of Participants who Achieved a Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36
		Percent BSA of BP Involvement from Baseline to Week 36	Change from Baseline to Week 36 in Percent BSA of BP Involvement
		BP180 Autoantibody IgG Titers from Baseline to Week 36	Change in BP180 Autoantibody IgG Titers from Baseline to Week 36
		ABQOL from Baseline to Week 36	Change in ABQOL from Baseline to Week 36
Database lock	18 February 2025		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set Week 36		
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300 mg Q2W**	**Placebo**
	Number of subjects	**53**	**53**

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
	Primary endpoint Proportion of Participants Achieving Sustained Remission at Week 36	18.3%	6.1%
Effect estimate per comparison	**Primary endpoint** Proportion of Participants Achieving Sustained Remission at Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo (95% CI)	12.2% (-0.79%, 26.10%)
		P-value	0.0645
Notes	Within group CIs were not calculated for estimated proportions For endpoints where CIs were not calculated, the corresponding 'variability statistic' table line has been removed		
Analysis description	**Secondary endpoint analysis**		
Analysis population and time point description	Full Analysis Set Week 36		
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 300 mg Q2W**	**Placebo**
	Number of subjects	**53**	**53**
	Key Secondary endpoint Percent Change in BPDAI Activity Score from Baseline to Week 36	-88.5	-73.6
	LS Mean % Change 95% CI	(-99.35, -77.74)	(-84.69, -62.53)
	Key Secondary endpoint Time to First Use of Rescue Medication (Days) up to Week 36	168.9	126.8
	Median Event Time (95% CI)	124.0 (114.00, NE)	113.5 (110.00, 115.00)

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
	Key Secondary endpoint Proportion of Participants with Improvement (Reduction) of Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36	71.7%	54.1%
	Key Secondary endpoint Percent Change in Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36	-66.7	-51.4
	LS Mean % Change 95% CI	(-80.31, -53.03)	(-64.90, -37.97)
	Key Secondary endpoint Total Cumulative Dose of OCS (mg) from Baseline to Week 36	4184.93	5121.15
	LS Mean 95% CI	(3282.643, 5087.221)	(4182.544, 6059.747)
	Secondary Endpoint Complete Remission (Days) While Not Requiring OCS up to Week 36	38.7	12.9
	LS Mean 95% CI	(23.20, 54.11)	(-2.91, 28.75)
	Secondary Endpoint Proportion of Participants with Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36	75.0%	53.0%
	Secondary Endpoint Percent BSA of BP Involvement from Baseline to Week 36	-24.07	-17.51

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
	LS Mean Change 95% CI	(-28.801, -19.348)	(-22.493, -12.520)
	Secondary Endpoint Change in BP180 Autoantibody IgG Titers from Baseline to Week 36	-162.80	-155.26
	LS Mean Change 95% CI	(-214.733, -110.865)	(-207.678, -102.838)
	Secondary Endpoint Mean Change in ABQOL from Baseline to Week 36	-7.09	-3.41
	LS Mean Change 95% CI	(-9.946, -4.231)	(-6.332, -0.485)
Effect estimate per comparison	**Key Secondary Endpoint** BPDAI Activity Score from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-14.9 (-28.36, -1.50)
		P-value	0.0293
	Key Secondary endpoint Time to use of Rescue Medication (Days) up to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Hazard Ratio (Dupilumab/Placebo) (95% CI)	0.48 (0.300, 0.770)
		P-value	0.0023
	Key Secondary endpoint Improvement in Weekly Average of Daily Peak Pruritus NRS ≥4 from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo (95% CI)	17.5% (-1.62%, 35.62%)
		P-value	0.0645
	Key Secondary endpoint Weekly Average of Daily Peak Pruritus NRS from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-15.2 (-32.21, -1.74)
		P-value	0.0785
	Key Secondary endpoint Total Cumulative Dose of OCS (mg) from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-936.21 (-2085.387, 212.961)
		P-value	0.1092

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Dupilumab in Adult Patients with Bullous Pemphigoid			
Study identifier	R668-BP-1902		
	Secondary Endpoint Complete Remission (Days) While Not Requiring OCS up to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	25.7 (5.85, 45.63)
		P-value	0.0112
	Secondary Endpoint Reduction in BPDAI Activity Score of at Least 90% from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo (95% CI)	22.0% (3.16%, 39.52%)
		P-value	0.0194
	Secondary Endpoint Percent BSA of BP Involvement from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-6.57 (-12.659, -0.478)
		P-value	0.0345
	Secondary Endpoint BP180 Autoantibody IgG Titers from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-7.54 (-67.140, 52.059)
		P-value	0.8042
	Secondary Endpoint ABQOL from Baseline to Week 36	**Comparison groups**	**Dupilumab 300 mg Q2W vs. Placebo**
		Difference vs. Placebo LS Mean (95% CI)	-3.68 (-7.320, -0.039)
		P-value	0.0476

5.3. Discussion on clinical efficacy

Data for clinical efficacy is based on the single pivotal study R668-BP-1902, a global, multicenter, randomized, double-blind, placebo controlled, parallel group phase 2/3 study to assess the efficacy and safety of dupilumab in adults with BP. No other phase 1 or phase 2 studies in BP prior to the conduct of the pivotal study were performed.

Patients received either dupilumab 300 mg SC, Q2W (including a loading dose of 600 mg) or placebo. This is the same dose regimen as for other dermatologic indications for which dupilumab is already approved (eg. atopic dermatitis and prurigo nodularis.

The following indication was initially claimed: "Dupixent is indicated for the treatment of adults with bullous pemphigoid (BP)". During the procedure, the indication was updated to "Dupixent is indicated for the treatment of adults with moderate-to-severe bullous pemphigoid (BP)."

Design and conduct of clinical studies

Study Design

The study included a 52-week double-blind treatment period, and a 12-week post-treatment follow-up. At baseline, all patients started treatment with a pre-defined regimen of oral corticosteroids depending on disease severity (0.5 mg/kg/day for BP patients with moderate and 0.75 mg/kg/day for patients with severe disease, respectively) with the aim to achieve rapid disease control within the first weeks. Disease control was defined as when new lesions ceased to form and existing lesions began to heal. Once stable disease control had been achieved during the first 6 weeks of treatment, oral corticosteroids were tapered with the objective to taper them off no later than by Week 16 as long as disease control was maintained. Patients who experienced a disease relapse (ie. appearance of 3 or more new lesions a month or at least 1 large eczematous lesion/urticarial plaque that does not heal within 1 week) during the taper or after taper completion could be rescued with oral or topical corticosteroids, non-steroidal immunosuppressive medications or biologics as per investigator's discretion. Of note, participants were allowed to continue study treatment if oral or topical corticosteroids were used while use of other rescued medication led to study drug discontinuation.

The definitions for disease control, remission and relapse were based on the extent of occurrence of new lesions and the healing/epithelialization of existing lesions and were based on established outcome definitions for this disease .

Study populations

The study enrolled adult patients, aged 18-90 years, with a confirmed diagnosis of BP and active disease and pruritus by means of the Bullous pemphigoid disease area index (BPDAI) ≥24 and a Peak pruritus NRS score for maximum itch intensity ≥4 at baseline. Treatment with systemic or topical corticosteroids was not allowed within 7 days, and within a period of 4 weeks for other immunosuppressive treatments such as mycophenolate mofetil, azathioprine, or methotrexate. Adequate washouts for prior treatment with biologics were defined in the exclusion criteria. Patients with prior treatment with IL-4 or IL-13 antagonists were excluded.

Endpoints

A composite endpoint ("patients achieving sustained remission") was used as primary endpoint which included patients who achieved complete remission (ie. absence of new lesions and epithelialization of old lesions) after corticosteroid tapering without need of any additional immunosuppressive treatments

and absence of any relapse or rescue medication during the entire 36-week treatment period. This endpoint represents a very favourable clinical outcome.

Other secondary endpoints aimed to evaluate the overall change in disease activity as measured by BPDAI and the change in pruritus symptoms as measured by the daily peak pruritus NRS.

To evaluate a steroid-sparing effect, secondary endpoints included evaluation of rescue medication use and the cumulative dose of OCS during treatment. Additional endpoints evaluated changes in serum autoantibody titers and in quality of life.

Sample size

The sample size was mathematically reproducible given the assumptions made by the MAH. However, it was noted that these assumptions were not well substantiated. A placebo rate for sustained remission of 35% was assumed and a rate of 75% (difference 40%) was assumed in the dupilumab arm. The assumptions were justified based on three publications (Joly, 2009; Simon, 2019; Abdat, 2020). Apparently, these assumptions were not met at all in the study where a placebo sustained remission rate of 6.1% and a dupilumab rate of 18.3% were observed. In retrospect, the assumed effect was too optimistic.

Randomisation and blinding

In principle the randomisation methods seem acceptable. It is noted, however, that the number of stratification factors was rather large given the small sample size. Outside of Japan, 3 binary factors were defined leading to a total of 8 strata. With an expected sample size of ~90 subjects this leaves only ~11 subjects (~5.5 per arm) per stratum, in the best case of balances strata. Stratifying for disease severity is considered highly relevant as the OCS dose differed in these strata. For this reason, the lack of stratification within Japan is not considered optimal. It was also noted that a rather high number of randomisation errors occurred: 6 (11.3%) in PBO and 7 (13.2%) in Dupilumab were allocated to the wrong stratum.

From the protocol it remained unclear if central study personnel such as statisticians were blinded. Only in the CSR it was stated that "any other sponsor and contract research organization personnel who are (…) involved in study conduct remain blinded". Appendix 16.1.13 of the CSR ("Study Administrative Structure") clarified that all Sponsor personnel including medical director, global patient safety lead, and study biostatistician were blinded until 13 Aug 2024. This provides some reassurance that relevant functions remained blinded until after the final protocol (PA3: 03 Mar 2024) and the final SAP (01 Aug 2024) were finalized.

Statistical analyses

The primary estimand primarily uses a composite strategy to include rescue therapy and treatment-related intercurrent events. In the rare case of other intercurrent events, a multiple imputation approach was used to impute values based on the allocated treatment arm. Sensitivity analyses including a tipping point analyses were pre-specified for missing data. This is considered acceptable. The analyses and estimands for binary secondary endpoints were defined in analogy to the primary endpoint and are endorsed. The analysis and estimand for the time to first rescue therapy is also considered acceptable.

The estimands and analyses for *continuous* endpoints are not always understandable and are not fully supported. To incorporate rescue therapy in the analysis of continuous endpoints, the "worst value from the closest visit" was to be used as of Protocol Amendment 3. In the protocol this was defined as follows:

"Worst value from the closest visit immediately prior to rescue treatment use (scheduled visit including baseline or unscheduled visit for BP relapse), on the visit of initiation of rescue treatment or afterwards up to week 36. Data are captured at visits; therefore, the worst value around and after the time of rescue treatment will be carried forward from one of the following until week 36 (whichever value is worst): the visit immediately prior to starting rescue treatment; or the visit when rescue treatment was started; or the visits after rescue treatment was started."

Upon request it was clarified that indeed the worst observation from the visit prior to rescue treatment through week 36 was used to impute all values after rescue therapy. The statement that the "worst value **closest to the visit**" was used to impute is hence not correct or at least is potentially misleading. The definition only differs from the WOCF definition by excluding earlier visits (which is maybe the reason for the inclusion of "closest to the visit"). The rationale for this strategy was that the worst value close to and after rescue therapy is "representative of the response that would be expected during the course of disease" given that the "need for rescue therapy indicates disease worsening". This is overall considered understandable. However, this estimate seems to target a hypothetical estimand ("if no rescue therapy was available at all"). This is an anti-conservative estimand in a sense that the treatment effect in this hypothetical scenario is clearly expected to be larger than with a treatment policy approach (effect regardless of rescue therapy.

The analysis of cumulative OCS dose apparently targets a hypothetical estimand strategy for non-OCS rescue therapies, i.e. the effect on OCS dose if no immunosuppressive medications or immunomodulating biologics were available. This is not a considered a clinically relevant estimand, as these treatments are available and are administered as needed. This estimand is considered anti-conservative as it inflates the treatment benefit in comparison to a meaningful treatment policy estimand.

Furthermore, non-OCS rescue therapies were then imputed using a WOCF approach from the time of the first non-OCS treatment onwards. All days after a non-OCS systemic rescue therapy was administered were imputed using the maximum dose a subject had previously received including baseline. This means that either the baseline OCS dose (ie. high-dose prednisone of 0.5 mg/kg/day or 0.75 mg/kg/day depending on baseline disease severity) or even higher doses were imputed. This approach was not clinically justified and does not seem to be a relevant estimate for the assumed targeted estimand. In the hypothetical scenario, a subject would not receive the same highest dose for an indefinite time if no proper disease control was achieved. In fact, in that case the OCS dose would be increased and tapering would be initiated as soon as clinically possible.

The hierarchical approach to control multiplicity across endpoints is in principle valid. It is noted, however, that the multiplicity control was defined for as many as 11 endpoints including "other secondary endpoints" and was defined in the SAP only. The protocol merely stated that *"The primary endpoint will be tested at a 2-sided 5% significance level. If the primary endpoint meets the significance level, the secondary endpoints will be tested at a 2-sided 5% significance level in the hierarchical testing procedure. The order of the hierarchy will be specified in the SAP."* While the Applicant states that this is in line with Regulation (EU) No 536/2014, Annex I, Section D, this is quite uncommon and not endorsed as it concerns a key feature of a clinical trial, which should usually be defined in the protocol.

The final order of hypotheses was not aligned with the order of endpoints as they were defined in the protocol. This might potentially indicate, that the initial order differed from the final order, which hence might have been defined in a data driven way. The Applicant confirmed upon request that the order was defined in the initial SAP (05 March 2024) while the study team remained blinded until primary analysis data base lock (13 August 2024).

Study conduct

The study was amended three times. Some of the changes meaningfully impacted the clinical trial (e.g. change of significance level, changes to the estimands and statistical analysis methods). Main protocol deviations pertained the use of excluded concomitant medications and use of corticosteroids as non-rescue treatment (in 24.5% of patients). Patients were classified as non-responder for the primary endpoint if corticosteroid use was assessed as affecting the efficacy.

A total of 163 participants were screened, and 106 participants were equally randomized to receive dupilumab (n=53) or placebo (n=53). A quite high number of participants failed screening due to not meeting the inclusion/exclusion criteria which mainly pertained not fulfilling the criteria BP diagnosis or reaching the required disease activity for inclusion. A total of 88 participants (82.1%) completed the 36-week treatment. A total of 82 participants (77.4%) completed the entire treatment period through week 52, while the remaining 24 participants (22.6%) discontinued before (dupilumab: 7; placebo 17).

Baseline data

As expected for the disease, the mean age was high (71.3 years) with 77.4% of patients with an age of ≥65 years. A total of 47.2% of patients where male. The duration of disease before enrolment was short with a mean/median duration of 0.95 or 0.30 years, respectively. This appears also reflected by the higher number of patients with new onset of disease as compared to relapsed disease (65.1% vs. 34.9%). The majority of patients had prior use of corticosteroids and/or other immunosuppressants (58.5%).

Overall, mean (SD) BPDAI activity score at baseline was 60.5 (29.99) with 66% of patients having disease activity defined as moderate (BPDAI: ≥24 to <60) and 34% of patients with severe disease activity (BPDAI: ≥60). Patients reported severe pruritis with a mean peak pruritus NRS score of 7.5. The mean (SD) affected body surface area by BP was 30.8% (20.37). A total of 27.4% of patients had mucosal involvement.

Efficacy data and additional analyses

Primary Endpoint

The study did not meet its primary endpoint. The proportion of patients achieving sustained remission at week 36 was (18.3%) as compared to placebo (6.1%) resulting in a difference of 12.2 percent points (95% CI: -0.79, 26.10; **p=0.0645**). The overall number of patients achieving the primary endpoint was low (dupilumab: 9; placebo: 3) which is attributable to the very stringent clinical definition of the endpoint but also indicates a lower than expected treatment effect for dupilumab (see *Sample size* above). A beneficial treatment effect in achieving complete remission without need for additional immunosuppressive treatment in a rather small set of patients may be suggested by these results, but it was not shown with sufficient statistical certainty.

As the primary endpoint is missed, this has substantial qualitative implication for the interpretation of the results for the primary endpoint itself but also for all other secondary endpoints. The study failed to demonstrate its main objective and given the applied multiple testing approach the type 1 error is not controlled anymore for all secondary endpoints thus compromising the study's overall data robustness (**MO**).

In addition, the primary endpoint first showed a significant result but was revised during the procedure based on inspection findings in two study sites comprising 9 of 106 enrolled patients. This leads to strong concerns regarding the studies overall data reliability. Additional details on study monitoring and on the issues identified in the two deficient sites were provided by the MAH which however could not convincingly justify that the overall study results for all patients are reliable. In particular, although

the MAH claims that monitoring, source data verification and audits were in place, these measures apparently were not able to identify the issues observed for the two identified deficient sites. The mere fact that a monitoring plan was in place does not allow any conclusion on the robustness of the data for the other 97 participants that were not inspected. The overall data reliability thus remains in doubt (**MO**).

Secondary Endpoints

Since the primary endpoint was not met, given the applied multiple testing approach, the type 1 error was not controlled for all secondary endpoint which largely impairs the overall robustness of the results. All results can only be regarded as descriptive and exploratory and not as statistically confirmative. Uncertainties with the overall data reliability as evidenced for the primary endpoint could also have impact impacted secondary endpoints.

An analysis based on a treatment policy strategy for the use of rescue treatment is considered the most informative to estimate the effect and are thus described below.

Use of rescue medication

Rescue medication was used for the first time especially in the placebo group towards the end of the taper period, indicating that the majority of placebo patients were not able to control their symptoms without additional immunosuppressive treatment. In contrast, use of rescue medication occurred less frequently in the dupilumab group. Nearly half of the patients (54.7%) in the dupilumab group had use of rescue medication as compared to 79.2% in the placebo group. Consequently, the mean time to the first use of a rescue medication was longer in the dupilumab group (168.9 days vs. 126.8 days). The lower use of rescue medication within the dupilumab group resulted in a nominal lower total cumulative OCS dose in the dupilumab group (3385.91 mg) as compared to placebo (4181.54 mg), with a mean difference of -795.63 mg at week 36 (using treatment policy strategy for non-OCS rescue medication use). This resulted in difference of approx. 5 mg in daily OCS dosing with approx. 4 mg taken in the dupilumab group and approx. 9 mg taken in the placebo group based on all observed OCS values which in principle can be seen as clinically relevant. However, the existing uncertainties in data robustness and data reliability need to be noted.

More non-OCS rescue therapies (1.75 per rescued dupliumab patient vs 1.125 per rescued placebo patient) were initiated at a substantially earlier point in time (median time of initiation in dupilumab 91.5 days vs 170.5 days in placebo) in dupliumab treated patients. In the primary estimand this still was imputed using WOCF leading to an anti-conservative estimate (i.e. in favour of placebo). While it is acknowledged that the data is too limited to draw firm conclusions, it adds to the uncertainty of the treatment effect for the primary estimand.

Change in disease activity and pruritus

After achievement of initial disease control, symptom improvements on the skin and, if present, on the mucosa as measured by BPDAI were mostly maintained in patients treated with dupilumab while an increasing disease activity was observed in the placebo group after the begin of the taper consistent with the observed higher use of rescue medication in this group. Based on a treatment policy analysis, the LS mean percent change from baseline in the total BPDAI activity score at week 36 was greater in the dupilumab group (-88.5% vs. -73.6%; difference -14.9). An additional responder analysis showed higher proportions of participants achieving a reduction in BPDAI activity score of at least 90% (ie, almost complete disease clearance) in the dupilumab group (71.7% vs 54.1%). Based on a treatment policy analysis, a total of 71.7% of patients in the dupilumab group had a reduction in the weekly average of daily peak pruritus NRS score ≥4 at week 36 as compared to 54.1% in the placebo group. The estimated effec on pruritus in BP seems lower as observed for other pruritic indications (e.g. atopic

dermatitis and prurigo nodularis) where dupilumab is also used. The effects seen at week 36 as described above were mostly maintained until week 52.

Overall, the estimated descriptive effects for the secondary endpoints suggest a treatment effect of dupilumab when used in addition to allowed oral and topical corticosteroids for rescue to maintain disease control with larger improvements in BP skin lesions and pruritus as compared to the control group. In other words, a better clinical outcome with less corticosteroid use may be achieved with dupilumab. This potential treatment effect of dupilumab is acknowledged. However, major limitations including lack of type 1 error control for all secondary endpoints and the rather moderate effect that is estimated with high uncertainty (large CIs) profoundly impair the robustness of the results. The results of the secondary endpoints are not considered sufficiently robust to compensate for the failed primary endpoint and to support demonstration of efficacy (**MO**).

Claimed indication

Based on the overall study design and objectives of the study, efficacy was investigated in patients with high disease activity (ie. moderate-to-severe disease) and the ability of dupilumab to taper off corticosteroids while maintaining disease remission was evaluated. While disease severity was initially not included in the sought indication, it is now reflected in the PI, in SmPC section 4.1 after EMA request.

SmPC

As presented and discussed above, BP patients required initial treatment with high-dose systemic corticosteroids to achieve rapid disease control. Additional use of corticosteroids after tapering was also needed in around half of dupilumab-treated patient. The initial and later (at least occasional) use of concomitant corticosteroids in addition to dupilumab is therefore clearly expected in a substantial number of BP patients treated with dupilumab. Adequate guidance on the concomitant use of corticosteroids is included in 4.2. The total cumulative OCS dose based on a treatment policy strategy is included in the labelling. To inform prescribers on the on the potential need of OCS and non-OCS rescue treatments next to dupilumab, a strongly simplified table summarizing use of all rescue medications has also been added.

5.4. Conclusions on the clinical efficacy

The results obtained in study R668-BP-1902 do not sufficiently support that dupilumab provides a benefit for patients with BP. The primary endpoint was not met and the robustness of the study results is largely compromised given the lack of type 1 error control for all secondary endpoints due to the applied multiplicity testing strategy. Only a moderate treatment effect for the secondary endpoints is estimated with large uncertainty. In addition, there are major concerns with the overall data reliability that could not be resolved with the MAHs response. A second confirmative study with a potentially adapted design is considered needed to clearly demonstrate dupilumabs treatment benefit in BP.

Overall, efficacy which is based on a single pivotal trial has not been sufficiently demonstrated and the extension of indication cannot be accepted (**MO**).

6. Clinical safety

Introduction

Dupilumab was first approved by the US FDA on 28 Mar 2017 for the treatment of adult and paediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis (AD). Furthermore, it is approved for the treatment of asthma in adults and paediatric patients aged 6 years and older, chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults, prurigo nodularis (PN) in adults, eosinophilic esophagitis (EoE) in adolescents and adults, COPD and CSU.

As outlined in the SmPC, the most common adverse reactions in atopic dermatitis, asthma, and CRSwNP are injection site reactions including erythema, oedema, pruritus, pain, induration, bruising and swelling, (allergic) conjunctivitis, arthralgia, oral herpes, and eosinophilia. Rare cases of serum sickness, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported (refer to SmPC section 4.4 and 4.8).

Patient exposure

Disposition

At the time of the primary data base lock, 65/106 patients completed study through week 52. The study ended globally on 05 January 2025 with 82/106 patients completing study through week 52.

A total of 106 participants were randomized to 1 of the 2 treatment groups: 53 participants to the placebo group and 53 participants to the dupilumab 300 mg Q2W group. Of the 106 randomized participants, all received study intervention and all had completed visits through week 36 of the treatment period or discontinued from the study before week 36. Additionally, at the time of data cutoff:

• 61.3% (65/106) of participants had completed visits through at least week 52 and 17.0% (18/106) of participants were ongoing (ie, between week 36 and week 52); the remaining had discontinued from the study before week 52

• 50.0% (53/106) participants had completed the study, including the post-treatment follow-up period, through week 64 and 7.5% (8/106) of participants were ongoing in the post-treatment follow-up period.

Study drug completion status and study visit completion status are described below. A total of 79.2% (42/53) of participants in the placebo group and 86.8% (46/53) of participants in the dupilumab 300 mg Q2W group completed the study through week 36 . 1 participant in the placebo group, who discontinued study drug before week 36 and remained on study until their early termination visit, had their early termination visit after the data cutoff date (but prior to the database lock date) and therefore this participant is counted as ongoing in the study before week 36. At the time of data cutoff, 67.9% (36/53) of participants in the placebo group and 86.8% (46/53) of participants in the dupilumab 300 mg Q2W group had completed the study through week 52 and 32.1% (17/53) and 13.2% (7/53) of participants, respectively, discontinued before week 52.

A total of 60.4% (32/53) of participants in the placebo group and 83.0% (44/53) of participants in the dupilumab 300 mg Q2W group received study drug through week 36; the remaining participants (21/53 [39.6%] in the placebo group and 9/53 [17.0%] in the dupilumab 300 mg Q2W group)

discontinued study drug before week 36. The higher rate of study drug discontinuation before week 36 in the placebo group was mostly driven by lack of efficacy (14 participants in the placebo group versus 5 participants in the dupilumab 300 mg Q2W group) and participant decision to discontinue (4 versus 1, respectively). AEs leading to study drug discontinuation before week 36 were reported in 2 participants in the placebo group and 3 participants in the dupilumab 300 mg Q2W group. At the time of data cutoff, 47.2% (28/53) of participants in the placebo group and 83.0% (44/53) of participants in the dupilumab 300 mg Q2W group completed study drug through week 52. Between weeks 36 and 52, 3 additional participants in the placebo group and no additional participants in the dupilumab 300 mg Q2W group discontinued study drug (total percentage of participants who discontinued study drug before week 52: 47.2% [25/53] in the placebo group and 17.0% [9/53] in the dupilumab 300 mg Q2W group). The 3 discontinuations in the placebo group between week 36 and week 52 were due to AEs.

Table 31. Disposition of Study Participants in Study R668-BP-1902 (All Randomised Participants)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants who completed study through week 36 [1]	42 (79.2%)	46 (86.8%)	88 (83.0%)
Participants who discontinued from study before week 36	11 (20.8%)	7 (13.2%)	18 (17.0%)
Reason for study discontinuation before week 36			
Due to COVID-19	0	0	0
Not Due to COVID-19	11 (100%)	7 (100%)	18 (100%)
Protocol Violation	0	0	0
Adverse Event	2 (18.2%)	2 (28.6%)	4 (22.2%)
Lack of Efficacy	4 (36.4%)	1 (14.3%)	5 (27.8%)
Physician Decision	0	1 (14.3%)	1 (5.6%)
Participant Decision	4 (36.4%)	3 (42.9%)	7 (38.9%)
Lost to Follow-up	0	0	0
Death	1 (9.1%)	0	1 (5.6%)
Other	0	0	0
Participants who completed study through week 52	36 (67.9%)	46 (86.8%)	82 (77.4%)
Participants who discontinued from study before week 52	17 (32.1%)	7 (13.2%)	24 (22.6%)
Reason for study discontinuation before week 52			
Due to COVID-19	0	0	0
Not Due to COVID-19	17 (100%)	7 (100%)	24 (100%)
Protocol Violation	0	0	0
Adverse Event	5 (29.4%)	2 (28.6%)	7 (29.2%)
Lack of Efficacy	5 (29.4%)	1 (14.3%)	6 (25.0%)
Physician Decision	0	1 (14.3%)	1 (4.2%)
Participant Decision	6 (35.3%)	3 (42.9%)	9 (37.5%)
Lost to Follow-up	0	0	0
Death	1 (5.9%)	0	1 (4.2%)
Other	0	0	0
Participants who completed study through week 64	32 (60.4%)	45 (84.9%)	77 (72.6%)
Participants who discontinued from study	21 (39.6%)	8 (15.1%)	29 (27.4%)
Reason for study discontinuation			
Due to COVID-19 [2]	1 (4.8%)	0	1 (3.4%)
Adverse Event	1 (4.8%)	0	1 (3.4%)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Not Due to COVID-19	20 (95.2%)	8 (100%)	28 (96.6%)
Protocol Violation	0	0	0
Adverse Event	5 (23.8%)	2 (25.0%)	7 (24.1%)
Lack of Efficacy	5 (23.8%)	1 (12.5%)	6 (20.7%)
Physician Decision	0	1 (12.5%)	1 (3.4%)
Participant Decision	8 (38.1%)	3 (37.5%)	11 (37.9%)
Lost to Follow-up	0	0	0
Death [2]	2 (9.5%)	1 (12.5%)	3 (10.3%)
Other	0	0	0
Participants who entered the study follow-up period (week 52 to week 64) [3]	35 (66.0%)	46 (86.8%)	81 (76.4%)

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; CSR=clinical study report; Q2W=every 2 weeks; SAE=serious adverse event.
Note: The percentage for reason for study discontinuation before each time point is calculated based on the number of participants who discontinued from the study before the time point in the respective treatment group.
[1] At the time of the Primary Analysis CSR Amendment 1 data cutoff date, 1 participant in the placebo group discontinued study drug before week 36 and remained on study until their early termination visit. The early termination visit occurred after the data cutoff date (but prior to the database lock date) for the Primary Analysis CSR Amendment 1, and therefore, this participant was counted as ongoing in the study before weeks 36, 52, and 64. As of the database lock date for this CSR addendum, the participant had completed the early termination visit and is now considered as having completed the study through week 36 and discontinued before week 52.
[2] At the time of the Primary Analysis CSR Amendment 1 data cutoff date, there were 2 participants in the placebo group who were considered as having discontinued the study between week 52 and week 64 due to death. As of the database lock date for this CSR addendum, follow-up information was received on 1) of these 2 participants, and the disposition status for this participant was updated to study discontinuation due to COVID-19-related AE.
[3] Participants who entered the study follow-up period are those who had at least one visit after the week 52 visit (or after the week 52 target date for those who did not complete the week 52 visit).

Table 32. Study Drug Completion Status and Primary Reason for Premature Discontinuation of the Study Drug in Study R668-BP-1902 (All Randomized Participants)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants who completed study drug through week 36	32 (60.4%)	44 (83.0%)	76 (71.7%)
Participants who discontinued study drug before week 36	21 (39.6%)	9 (17.0%)	30 (28.3%)
Reason for study drug discontinuation before week 36			
Due to COVID-19	0	0	0
Not Due to COVID-19	21 (100%)	9 (100%)	30 (100%)
Protocol Violation	0	0	0
Adverse Event	2 (9.5%)	3 (33.3%)	5 (16.7%)
Pregnancy	0	0	0
Lack of Efficacy	14 (66.7%)	5 (55.6%)	19 (63.3%)
Physician Decision	0	0	0
Subject Decision	4 (19.0%)	1 (11.1%)	5 (16.7%)
Lost to Follow-up	0	0	0
Death	1 (4.8%)	0	1 (3.3%)
Other	0	0	0
Participants who completed study drug through week 52	28 (52.8%)	44 (83.0%)	72 (67.9%)
Participants who discontinued study drug before week 52	25 (47.2%)	9 (17.0%)	34 (32.1%)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Reason for study drug discontinuation before week 52			
Due to COVID-19 [1]	1 (4.0%)	0	1 (2.9%)
Adverse Event	1 (4.0%)	0	1 (2.9%)
Not Due to COVID-19	24 (96.0%)	9 (100%)	33 (97.1%)
Protocol Violation	0	0	0
Adverse Event	5 (20.0%)	3 (33.3%)	8 (23.5%)
Pregnancy	0	0	0
Lack of Efficacy	14 (56.0%)	5 (55.6%)	19 (55.9%)
Physician Decision	0	0	0
Participant Decision	4 (16.0%)	1 (11.1%)	5 (14.7%)
Lost to Follow-up	0	0	0
Death	1 (4.0%)	0	1 (2.9%)
Other	0	0	0

Abbreviations: COVID-19=coronavirus disease 2019; CRF=case report form; Q2W=every 2 weeks; SAE=serious adverse event.
Note: The percentage for reason for study drug discontinuation before each time point is calculated based on the number of participants who discontinued from study drug before the time point in the respective treatment group. Of note, if a participant received rescue treatment with a systemic non-steroidal immunosuppressive drug or immunomodulating biologic, study drug was to be permanently discontinued immediately.
[1] In the Primary Analysis CSR Amendment 1, 1 participant in the placebo group discontinued from the study drug due to an SAE of COVID-19. However, the Supplemental form - Study/Treatment Discontinuation due to COVID-19 CRF was not completed, so the study drug discontinuation was not flagged as being COVID-19-related and was designated as study drug discontinuation due to adverse event. As of the database lock date for this CSR addendum, follow-up information was received, and the study drug disposition status for this participant was updated to discontinuation due to COVID-19-related adverse event

Exposure

The mean (SD) number of study drug administrations (injections) per participant was 19.3 (8.16) in the placebo group and 22.5 (7.36) in the dupilumab 300 mg Q2W group. The mean (SD) duration of treatment exposure was 296.7 (111.40) days: 273.5 (113.80) days in the placebo group and 320.0 (104.90) days in the dupilumab 300 mg Q2W group.

Table 33. Study Drug Administration, Treatment Exposure, and Duration of Observation Period in Study R668-BP1902 (SAF)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Number of administrations of study drug			
n	53	53	106
Mean (SD)	19.3 (8.16)	22.5 (7.36)	20.9 (7.89)
Median	25.0	26.0	26.0
Q1 : Q3	12.0 : 26.0	25.0 : 26.0	16.0 : 26.0
Min : Max	1 : 26	3 : 26	1 : 26
Cumulative number of administrations of study drug, n (%)			
≥1	53 (100%)	53 (100%)	106 (100%)
≥2	52 (98.1%)	53 (100%)	105 (99.1%)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
≥3	51 (96.2%)	53 (100%)	104 (98.1%)
≥4	51 (96.2%)	51 (96.2%)	102 (96.2%)
≥5	50 (94.3%)	51 (96.2%)	101 (95.3%)
≥6	49 (92.5%)	50 (94.3%)	99 (93.4%)
≥7	48 (90.6%)	49 (92.5%)	97 (91.5%)
≥8	46 (86.8%)	48 (90.6%)	94 (88.7%)
≥9	46 (86.8%)	45 (84.9%)	91 (85.8%)
≥10	44 (83.0%)	45 (84.9%)	89 (84.0%)
≥11	43 (81.1%)	45 (84.9%)	88 (83.0%)
≥12	41 (77.4%)	45 (84.9%)	86 (81.1%)
≥13	39 (73.6%)	44 (83.0%)	83 (78.3%)
≥14	38 (71.7%)	44 (83.0%)	82 (77.4%)
≥15	36 (67.9%)	44 (83.0%)	80 (75.5%)
≥16	36 (67.9%)	44 (83.0%)	80 (75.5%)
≥17	33 (62.3%)	44 (83.0%)	77 (72.6%)
≥18	33 (62.3%)	44 (83.0%)	77 (72.6%)
≥19	32 (60.4%)	44 (83.0%)	76 (71.7%)
≥20	32 (60.4%)	44 (83.0%)	76 (71.7%)
≥21	30 (56.6%)	43 (81.1%)	73 (68.9%)
≥22	30 (56.6%)	43 (81.1%)	73 (68.9%)
≥23	30 (56.6%)	42 (79.2%)	72 (67.9%)
≥24	29 (54.7%)	42 (79.2%)	71 (67.0%)
≥25	27 (50.9%)	42 (79.2%)	69 (65.1%)
≥26	24 (45.3%)	38 (71.7%)	62 (58.5%)
≥27	0	0	0

Abbreviations: Max=maximum; Min=minimum; Q1=first quartile; Q2W=every 2 weeks; Q3=third quartile; SAF=safety analysis set; SD=standard deviation.
Note: The loading doses of study drug administered on Day 1 are counted as a single administration of study drug.

Table 34. Treatment Exposure and Duration of Observation (SAF)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Duration of treatment exposure (days)			
n	53	53	106
Mean (SD)	273.5 (113.80)	320.0 (104.90)	296.7 (111.40)
Median	361.0	364.0	363.0
Q1 : Q3	173.0 : 364.0	363.0 : 365.0	224.0 : 364.0
Min : Max	14 : 378	41 : 441	14 : 441
Duration of participant observation (days)			
n	53	53	106
Mean (SD)	361.2 (142.10)	412.7 (117.52)	386.9 (132.32)
Median	447.0	449.0	449.0
Q1 : Q3	288.0 : 449.0	448.0 : 451.0	405.0 : 450.0
Min : Max	1 : 512	28 : 665 [1]	1 : 665 [1]

Abbreviations: Max=maximum; Min=minimum; Q1=first quartile; Q2W=every 2 weeks; Q3=third quartile; SAF=safety analysis set; SD=standard deviation.
Note: Duration of treatment exposure is defined as: (Date of last study drug injection - date of first study drug injection) + 14. Duration of participant observation is defined as: (Date of last visit - date of first study drug injection) + 1.
[1] End-of-study visit was significantly delayed for 1 participant due to the occurrence of a road traffic accident which occurred during the follow-up period.

Demographic and Other Characteristics of Study Population

Demographic characteristics of participants are shown in the Table 35 below.

Table 35. Demographics (FAS)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Age (years)			
n	53	53	106
Mean (SD)	71.5 (9.52)	71.2 (10.01)	71.3 (9.72)
Median	73.0	72.0	72.0
Q1 : Q3	66.0 : 78.0	65.0 : 79.0	65.0 : 79.0
Min : Max	42 : 87	48 : 89	42 : 89
Age group, n (%)			
<65 years	11 (20.8%)	13 (24.5%)	24 (22.6%)
≥65 years	42 (79.2%)	40 (75.5%)	82 (77.4%)
≥65 to <75 years	20 (37.7%)	18 (34.0%)	38 (35.8%)
≥75 years	22 (41.5%)	22 (41.5%)	44 (41.5%)
Ethnicity, n (%)			
Hispanic or Latino	3 (5.7%)	0	3 (2.8%)
Not Hispanic or Latino	42 (79.2%)	43 (81.1%)	85 (80.2%)
Unknown	1 (1.9%)	2 (3.8%)	3 (2.8%)
Not Reported	7 (13.2%)	8 (15.1%)	15 (14.2%)
Race, n (%)			
White	37 (69.8%)	35 (66.0%)	72 (67.9%)

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Black or African American	1 (1.9%)	1 (1.9%)	2 (1.9%)
Asian	7 (13.2%)	9 (17.0%)	16 (15.1%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	2 (3.8%)	0	2 (1.9%)
Not Reported	6 (11.3%)	8 (15.1%)	14 (13.2%)
Region (IWRS), n (%) [1]			
North America	12 (22.6%)	12 (22.6%)	24 (22.6%)
Europe	35 (66.0%)	37 (69.8%)	72 (67.9%)
Japan	6 (11.3%)	4 (7.5%)	10 (9.4%)
Region, n (%) [1]			
North America	12 (22.6%)	12 (22.6%)	24 (22.6%)
Europe	34 (64.2%)	32 (60.4%)	66 (62.3%)
Asia	7 (13.2%)	9 (17.0%)	16 (15.1%)
Country, n (%)			
Australia	3 (5.7%)	2 (3.8%)	5 (4.7%)
France	7 (13.2%)	8 (15.1%)	15 (14.2%)
Germany	18 (34.0%)	16 (30.2%)	34 (32.1%)
Israel	2 (3.8%)	3 (5.7%)	5 (4.7%)
Japan	6 (11.3%)	4 (7.5%)	10 (9.4%)
Poland	2 (3.8%)	2 (3.8%)	4 (3.8%)
Spain	2 (3.8%)	1 (1.9%)	3 (2.8%)
Taiwan	1 (1.9%)	5 (9.4%)	6 (5.7%)
United States	12 (22.6%)	12 (22.6%)	24 (22.6%)
Sex, n (%)			
Male	29 (54.7%)	21 (39.6%)	50 (47.2%)
Female	24 (45.3%)	32 (60.4%)	56 (52.8%)
Height (cm)			
n	53	53	106
Mean (SD)	166.66 (10.275)	166.36 (11.901)	166.51 (11.066)
Median	168.50	167.00	168.00
Q1 : Q3	158.00 : 174.00	156.00 : 174.00	157.00 : 174.00
Min : Max	147.1 : 188.0	140.0 : 200.0	140.0 : 200.0
Weight (kg)			
n	53	53	106
Mean (SD)	78.35 (15.766)	76.57 (20.439)	77.46 (18.187)
Median	79.00	75.00	76.00
Q1 : Q3	68.90 : 90.00	63.50 : 85.00	65.30 : 90.00
Min : Max	39.8 : 118.0	40.4 : 150.0	39.8 : 150.0
Weight group, n (%)			

	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
<60 kg	6 (11.3%)	9 (17.0%)	15 (14.2%)
≥60 to <90 kg	33 (62.3%)	31 (58.5%)	64 (60.4%)
≥90 kg	14 (26.4%)	13 (24.5%)	27 (25.5%)
BMI (kg/m^2)			
n	53	53	106
Mean (SD)	28.27 (5.774)	27.51 (6.141)	27.89 (5.944)
Median	27.60	27.20	27.20
Q1 : Q3	24.80 : 32.00	23.20 : 30.20	23.50 : 31.20
Min : Max	18.4 : 46.7	17.9 : 48.8	17.9 : 48.8
BMI group, n (%)			
<15 kg/m^2	0	0	0
≥15 to <25 kg/m^2	15 (28.3%)	17 (32.1%)	32 (30.2%)
≥25 to <30 kg/m^2	21 (39.6%)	22 (41.5%)	43 (40.6%)
≥30 kg/m^2	17 (32.1%)	14 (26.4%)	31 (29.2%)

Percentages are based on the number of randomized participants in each treatment group as denominator.
[1] Regions for stratification were as follows: North America vs. Europe (including Australia, Israel and Taiwan) vs. Japan. Regions used for subgroup analyses were as follows: North America vs. Europe (including Australia and Israel) vs. Asia (Taiwan and Japan).
Abbreviations: BMI=body mass index; FAS=full analysis set; IWRS=interactive web response system; Q2W=every 2 weeks.
Source: PTT 14.1.2.1

The medical history is shown in Table 36 below.

Table 36. Medical History by SOC and PT in Study R668-BP-1902 (SOC Findings Reported in ≥20% or PT Findings Reported in ≥5% of the Total Population; FAS)

System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants with at least one medical history finding	53 (100%)	53 (100%)	106 (100%)
Skin and subcutaneous tissue disorders	53 (100%)	53 (100%)	106 (100%)
Pemphigoid	53 (100%)	53 (100%)	106 (100%)
Vascular disorders	41 (77.4%)	37 (69.8%)	78 (73.6%)
Hypertension	38 (71.7%)	35 (66.0%)	73 (68.9%)
Metabolism and nutrition disorders	30 (56.6%)	35 (66.0%)	65 (61.3%)
Type 2 diabetes mellitus	13 (24.5%)	5 (9.4%)	18 (17.0%)
Hypercholesterolaemia	8 (15.1%)	9 (17.0%)	17 (16.0%)
Hyperlipidaemia	6 (11.3%)	10 (18.9%)	16 (15.1%)
Diabetes mellitus	4 (7.5%)	10 (18.9%)	14 (13.2%)
Dyslipidaemia	4 (7.5%)	2 (3.8%)	6 (5.7%)
Gout	2 (3.8%)	4 (7.5%)	6 (5.7%)
Obesity	5 (9.4%)	1 (1.9%)	6 (5.7%)

System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Surgical and medical procedures	25 (47.2%)	27 (50.9%)	52 (49.1%)
Hysterectomy	4 (7.5%)	6 (11.3%)	10 (9.4%)
Cholecystectomy	3 (5.7%)	4 (7.5%)	7 (6.6%)
Hip arthroplasty	3 (5.7%)	4 (7.5%)	7 (6.6%)
Appendicectomy	4 (7.5%)	2 (3.8%)	6 (5.7%)
Cataract operation	1 (1.9%)	5 (9.4%)	6 (5.7%)
Thyroidectomy	2 (3.8%)	4 (7.5%)	6 (5.7%)
Musculoskeletal and connective tissue disorders	20 (37.7%)	23 (43.4%)	43 (40.6%)
Osteoarthritis	8 (15.1%)	4 (7.5%)	12 (11.3%)
Osteoporosis	1 (1.9%)	7 (13.2%)	8 (7.5%)
Nervous system disorders [1]	19 (35.8%)	20 (37.7%)	39 (36.8%)
Infections and infestations [1]	16 (30.2%)	14 (26.4%)	30 (28.3%)
Cardiac disorders	13 (24.5%)	15 (28.3%)	28 (26.4%)
Atrial fibrillation	7 (13.2%)	4 (7.5%)	11 (10.4%)
Gastrointestinal disorders	14 (26.4%)	14 (26.4%)	28 (26.4%)
Gastrooesophageal reflux disease	7 (13.2%)	3 (5.7%)	10 (9.4%)
Psychiatric disorders	13 (24.5%)	13 (24.5%)	26 (24.5%)
Depression	4 (7.5%)	5 (9.4%)	9 (8.5%)
Insomnia	4 (7.5%)	4 (7.5%)	8 (7.5%)
Anxiety	4 (7.5%)	3 (5.7%)	7 (6.6%)
Respiratory, thoracic and mediastinal disorders	11 (20.8%)	15 (28.3%)	26 (24.5%)
Asthma	2 (3.8%)	6 (11.3%)	8 (7.5%)
Chronic obstructive pulmonary disease	1 (1.9%)	6 (11.3%)	7 (6.6%)
Eye disorders	9 (17.0%)	14 (26.4%)	23 (21.7%)
Cataract	6 (11.3%)	9 (17.0%)	15 (14.2%)
Renal and urinary disorders	7 (13.2%)	14 (26.4%)	21 (19.8%)
Renal failure	3 (5.7%)	3 (5.7%)	6 (5.7%)
Endocrine disorders	12 (22.6%)	8 (15.1%)	20 (18.9%)
Hypothyroidism	9 (17.0%)	6 (11.3%)	15 (14.2%)
Reproductive system and breast disorders	10 (18.9%)	5 (9.4%)	15 (14.2%)
Benign prostatic hyperplasia	8 (15.1%)	4 (7.5%)	12 (11.3%)
Immune system disorders	8 (15.1%)	4 (7.5%)	12 (11.3%)
Seasonal allergy	4 (7.5%)	3 (5.7%)	7 (6.6%)
Drug hypersensitivity	3 (5.7%)	3 (5.7%)	6 (5.7%)

A participant who reported 2 or more medical history findings with the same PT is counted only once for that term. A participant who reported 2 or more medical history findings with different PTs within the same system organ class is counted only once for that SOC.
MedDRA (Version 27.0) coding dictionary applied.
[1] For the SOCs of Nervous system disorders and Infections and infestations, no specific PTs were reported in ≥5% of participants.
Abbreviations: FAS=full analysis set; PT=preferred term; Q2W=every 2 weeks; SOC=system organ class.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.1.2.3

Overall, 98.1% (104/106) of participants reported at least 1 prior medication for conditions other than BP . Overall, 94.3% (100/106) of participants had used at least 1 prior medication for BP.

The most frequently reported prior medications for BP by therapeutic class were:

• Corticosteroids, dermatological preparations (placebo: 73.6% [39/53]; dupilumab 300 mg Q2W: 75.5% [40/53] [almost entirely topical corticosteroids]). Of the topical corticosteroids, the very potent (Group IV) preparations (eg, clobetasol) were the most frequently used (placebo: 41.5% [22/53]; dupilumab 300 mg Q2W: 43.4% [23/53])

• Corticosteroids for systemic use (placebo: 64.2% [34/53]; dupilumab 300 mg Q2W: 62.3% [33/53])

• Antihistamines for systemic use (placebo: 34.0% [18/53]; dupilumab 300 mg Q2W: 37.7% [20/53])

• Antibacterials for systemic use (including the tetracycline class of antibiotics, eg, doxycycline) (placebo: 24.5% [13/53]; dupilumab 300 mg Q2W: 20.8% [11/53]).

Table 37. Prior Medications for BP by Therapeutic Class (Reported in ≥5% of the Total Population; FAS)

ATC Level 2	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Total (N=106)
Participants with at least one prior medication for bullous pemphigoid	51 (96.2%)	49 (92.5%)	100 (94.3%)
Corticosteroids, dermatological preparations [1]	39 (73.6%)	40 (75.5%)	79 (74.5%)
Corticosteroids for systemic use	34 (64.2%)	33 (62.3%)	67 (63.2%)
Antihistamines for systemic use	18 (34.0%)	20 (37.7%)	38 (35.8%)
Antibacterials for systemic use [2]	13 (24.5%)	11 (20.8%)	24 (22.6%)
Immunosuppressants [3]	6 (11.3%)	13 (24.5%)	19 (17.9%)
Emollients and protectives	7 (13.2%)	8 (15.1%)	15 (14.2%)
Analgesics	3 (5.7%)	6 (11.3%)	9 (8.5%)
Antipruritic, incl. antihistamines, anesthetics, etc.	2 (3.8%)	7 (13.2%)	9 (8.5%)
Antibiotics and chemotherapeutics for dermatological use	1 (1.9%)	7 (13.2%)	8 (7.5%)
Antimycotics for systemic use [4]	4 (7.5%)	4 (7.5%)	8 (7.5%)
Drugs for acid related disorders	2 (3.8%)	5 (9.4%)	7 (6.6%)
Psycholeptics	2 (3.8%)	5 (9.4%)	7 (6.6%)

WHODrug-Global-B3 dictionary applied.
A participant for whom 2 or more medications with different standardized medication names within the same ATC level have been reported is counted only once for that ATC level.
The table is sorted by descending order of frequency of ATC level 2 in the total group.
[1] This category consists almost entirely of topical corticosteroids
[2] Includes tetracycline class of antibiotics used for BP (eg, doxycycline)
[3] Includes systemic immunosuppressants or biologics (eg, methotrexate, mycophenolate mofetil, azathioprine, tofacitinib)
[4] Includes dapsone
Abbreviations: ATC=Anatomical Therapeutic Chemical; FAS=full analysis set; Q2W=every 2 weeks.
Source: PTT 14.1.3.2

Adverse events

Overview of Adverse Events

At the time of the initial submission study R668-BP-1902 was still ongoing with 65/106 patients completing study through week 52 at the time of the primary data base lock. The applicant provided a CSR addendum presenting all cumulative safety data from study R668-BP-1902 (see Table 38 below). The results were consistent with the primary analysis.

Table 38. Overall Summary of Number of Participants with Treatment-Emergent Adverse Events During the On-Treatment Period Through Week 52 (Primary Analysis and Final Analysis) (SAF)

	Primary Analysis		Final Analysis	
	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
TEAE	51 (96.2%)	51 (96.2%)	51 (96.2%)	51 (96.2%)
TEAE with severity				
Mild	19 (35.8%)	15 (28.3%)	19 (35.8%)	15 (28.3%)
Moderate	20 (37.7%)	27 (50.9%)	20 (37.7%)	27 (50.9%)
Severe	12 (22.6%)	9 (17.0%)	12 (22.6%)	9 (17.0%)
TE-SAE	16 (30.2%)	12 (22.6%)	16 (30.2%)	12 (22.6%)
Treatment-related TEAE	8 (15.1%)	14 (26.4%)	8 (15.1%)	14 (26.4%)
Treatment-related TE-SAE	0	0	0	0
TEAE leading to study drug discontinuation	5 (9.4%)	2 (3.8%)	6 (11.3%)	3 (5.7%)
TEAE leading to death	2 (3.8%)	0	1 (1.9%) [1]	0 [1]

Abbreviations: Q2W=every 2 weeks; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.
[1] The number of participants with fatal SAEs during the on-treatment period through week 52 decreased from 2 participants in the primary analysis to 1 participant in the final analysis due to receiving follow-up information for 1 participant in the placebo group who died due to Respiratory failure. In the primary analysis, the Respiratory failure event was considered to have an onset during the on-treatment period. Since the primary analysis, the start month of the SAE leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52. As such, the event is no longer included in event counts during the on-treatment period through week 52.
Participants who experienced more than 1 TEAE were counted only once in each category.

Table 39. Overview of the Number of Participants (per 100 Participant-Years) with Treatment-Emergent Adverse Events During the On-Treatment Period Through Week 52 (Primary Analysis and Final Analysis) (SAF)

	Primary Analysis		Final Analysis	
Participants with at least one	**Placebo (N=53) nP/PY (nP/100 PY)**	**Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)**	**Placebo (N=53) nP/PY (nP/100 PY)**	**Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)**
TEAE	51/7.5 (679.35)	51/9.5 (534.51)	51/7.5 (679.35)	51/9.5 (534.51)
Moderate or severe TEAE	32/23.0 (139.08)	36/21.1 (170.43)	32/23.3 (137.60)	36/21.6 (166.82)
Severe TEAE	12/35.4 (33.94)	9/39.6 (22.73)	12/36.0 (33.37)	9/40.8 (22.08)
TE-SAE	16/34.6 (46.22)	12/38.8 (30.92)	16/35.1 (45.62)	12/39.8 (30.12)

	Primary Analysis		Final Analysis	
Participants with at least one	**Placebo (N=53) nP/PY (nP/100 PY)**	**Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)**	**Placebo (N=53) nP/PY (nP/100 PY)**	**Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)**
Treatment-related TEAE	8/34.0 (23.54)	14/36.1 (38.74)	8/34.1 (23.44)	14/37.5 (37.35)
TEAE leading to study drug discontinuation	5/39.2 (12.75)	2/45.1 (4.43)	6/39.7 (15.12)	3/46.5 (6.45) [2]
TEAE leading to death	2/39.0 (5.13)	0/45.2 (0.00)	1/39.8 (2.51) [1]	0/46.6 (0.00)

Abbreviations: nP=number of participants with an event; nP/100 PY=number of participants with at least 1 event per 100 participant-years; PY=participant-years; Q2W=every 2 weeks; SAE=serious adverse event; SAF=safety analysis set; TE=treatment-emergent; TEAE=treatment-emergent adverse event.
For participants with the given event, the number of participant-years is calculated up to the date of the first such event; for participants without the given event, the number of participant-years corresponds to the length of the treatment period. Participants who experienced more than 1 TEAE were counted only once in each category.
[1] The number of participants with fatal SAEs during the on-treatment period through week 52 decreased from 2 participants in the primary analysis to 1 participant in the final analysis due to receiving follow-up information for 1 participant in the placebo group who died due to Respiratory failure. In the primary analysis, the Respiratory failure event was considered to have an onset during the on-treatment period. Since the primary analysis, the start month of the SAE leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52. As such, the event is no longer included in event counts during the on-treatment period through week 52.
[2] One event in the dupilumab 300 mg Q2W group (Cardiac arrest) occurred before the primary analysis data cutoff date. This event was considered as not treatment-emergent at that time, because it occurred 2 days after the end-of-study date. As of the CSR addendum database lock date, the end-of-study visit date for this participant was updated to occur approximately 2 months later, which resulted in re-classification of the event as treatment-emergent occurring during the on-treatment period through week 52.

Common Treatment-Emergent Adverse Events

A summary of TEAEs reported by ⩾ 5% of participants in any treatment group in the on-treatment period through week 52 sorted by preferred terms (PTs) are included in the Table 40 below.

No new safety concerns were identified as regards the analysis of the safety data of all study participants who completed the study through week 52, i. e. since the primary analysis CSR. The proportion of participants who experienced at least 1 TEAE during the on-treatment period through week 52 was the same in each treatment group (96.2%) and was unchanged from the proportions reported in the primary analysis. Since the primary analysis, the proportion of participants with treatment-emergent treatment-related AEs, treatment-emergent serious adverse events (TE-SAEs), and severe TEAEs remained the same in both treatment groups during the on-treatment period through week 52.

Table 40. Summary of Treatment-Emergent Adverse Events Reported by ⩾5% of Participants in any Treatment Group During the On-Treatment Period Through Week 52 by Primary SOC and PT (SAF)

Primary System Organ Class Preferred Term	**Placebo (N=53)**	**Dupilumab 300 mg Q2W (N=53)**
Number of participants with at least 1 TEAE	51 (96.2%)	51 (96.2%)
Infections and infestations	27 (50.9%)	28 (52.8%)
Nasopharyngitis	8 (15.1%)	7 (13.2%)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Conjunctivitis	0	4 (7.5%)
COVID-19	3 (5.7%)	3 (5.7%)
Upper respiratory tract infection	1 (1.9%)	3 (5.7%)
Oral candidiasis	3 (5.7%)	2 (3.8%)
Cellulitis	3 (5.7%)	0
Gastroenteritis	3 (5.7%)	0
Skin and subcutaneous tissue disorders	26 (49.1%)	25 (47.2%)
Pemphigoid	12 (22.6%)	6 (11.3%)
Pruritus	4 (7.5%)	3 (5.7%)
Intertrigo	3 (5.7%)	0
Gastrointestinal disorders	17 (32.1%)	19 (35.8%)
Diarrhoea	6 (11.3%)	6 (11.3%)
Constipation	1 (1.9%)	4 (7.5%)
Abdominal pain upper	3 (5.7%)	2 (3.8%)
Nausea	3 (5.7%)	1 (1.9%)
Injury, poisoning and procedural complications	15 (28.3%)	17 (32.1%)
Fall	8 (15.1%)	6 (11.3%)
Limb injury	2 (3.8%)	3 (5.7%)
Musculoskeletal and connective tissue disorders	11 (20.8%)	17 (32.1%)
Arthralgia	3 (5.7%)	5 (9.4%)
Back pain	2 (3.8%)	4 (7.5%)
General disorders and administration site conditions	13 (24.5%)	13 (24.5%)
Oedema peripheral	5 (9.4%)	8 (15.1%)
Nervous system disorders	14 (26.4%)	13 (24.5%)
Headache	5 (9.4%)	4 (7.5%)
Metabolism and nutrition disorders	13 (24.5%)	12 (22.6%)
Hyperglycaemia	4 (7.5%)	2 (3.8%)
Decreased appetite	4 (7.5%)	0
Eye disorders	8 (15.1%)	10 (18.9%)
Vision blurred	0	4 (7.5%)
Cataract	4 (7.5%)	1 (1.9%)
Vascular disorders	9 (17.0%)	10 (18.9%)
Hypertension	3 (5.7%)	4 (7.5%)
Respiratory, thoracic and mediastinal disorders	9 (17.0%)	9 (17.0%)
Asthma	1 (1.9%)	4 (7.5%)
Dyspnoea	3 (5.7%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (11.3%)	6 (11.3%)
Basal cell carcinoma	3 (5.7%)	1 (1.9%)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Psychiatric disorders	6 (11.3%)	6 (11.3%)
Insomnia	2 (3.8%)	3 (5.7%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
MedDRA (Version 27.1) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.

Severity of Treatment-Emergent Adverse Events

A summary of severe TEAEs that were reported through week 52 is shown in the Table 41 below.

One case of severe drug-induced liver injury (VT: acute drug-induced hepatitis) was reported in the dupilumab 300 mg Q2W group: The participant had a pre-treatment AE of Hepatic function abnormal on study day -5 which was assessed as moderate in severity. On study day -1, the participant had elevated ALT (103 IU/L [normal range: 10-33]) and AST (46 IU/L [normal range: 10-36]). On study day 3, ALT and AST were 237 IU/L and 167 IU/L, respectively. By week 4, both parameters were within the normal range with further minor elevations at week 36 (ALT only) and week 52 (ALT and AST) which normalized again at week 64 (end of study). Bilirubin values were within the normal range at all visits. The participant continued dupilumab 300 mg Q2W for the duration of the 52-week treatment period. The following medications were initiated within 2 weeks prior to the pre-treatment AE of Hepatic function abnormal: alprazolam (study day -9 to 4), enoxaparin sodium (study day -9 to 14), pantoprazole (study day -9 to 448), paracetamol (study day -9 to 15), calcium carbonate (study day -8 to 448), lidocaine (study day -8 to 14), and oxycodone (study day -5 to 13). The participant did not have a medical history of hepatobiliary disorders or substance abuse. The TEAE of Drug-induced liver injury was assessed as unrelated to study drug by the investigator and reported as resolved without treatment. Alprazolam was discontinued on study day 4 because of the event, but the investigator was unsure of the direct causality.

Since the Primary Analysis CSR Amendment 1, updates were received on 2 participants that changed the overall proportions of participants with SAEs during the on-treatment period through week 52 by individual PT. These cases are briefly summarized below:

- 1 severe TE-SAE of Cardiac arrest in the dupilumab 300 mg Q2W group was considered as not treatment-emergent at the time of the Primary Analysis CSR Amendment 1 cutoff date, because it occurred 2 days after the end-of-study visit date. Since the primary analysis, the end-of-study visit date for this participant was updated to occur approximately 2 months later, which resulted in re-classification of the event as treatment-emergent during the on-treatment period through week 52, and the event is now included in Table 41.
- 1 event of Respiratory failure in the placebo group was presented as a severe SAE during the on-treatment period through week 52 in the Primary Analysis CSR Amendment 1. Due to follow-up information received after the Primary Analysis CSR Amendment 1 cutoff date, the event was determined to have occurred during the follow-up period and not during the on-treatment period through week 52 as stated in the Primary Analysis CSR Amendment 1. As such, the event is no longer included in Table 41.

Table 41. Summary of Severe TEAEs During the On-Treatment Period Through Week 52 by Primary SOC and PT (SAF)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of participants with at least 1 severe TEAE	12 (22.6%)	9 (17.0%)
Infections and infestations	4 (7.5%)	3 (5.7%)
Arthritis bacterial	0	1 (1.9%)
COVID-19	1 (1.9%)	0
Pneumonia	0	1 (1.9%)
Urinary tract infection	1 (1.9%)	0
Post procedural infection	0	1 (1.9%)
Urosepsis	0	1 (1.9%)
Cellulitis	1 (1.9%)	0
Erysipelas	1 (1.9%)	0
Injury, poisoning and procedural complications	2 (3.8%)	2 (3.8%)
Fall	1 (1.9%)	2 (3.8%)
Spinal fracture	0	1 (1.9%)
Procedural pain	1 (1.9%)	0
Metabolism and nutrition disorders	3 (5.7%)	1 (1.9%)
Hyperglycaemia	1 (1.9%)	0
Hypernatraemia	0	1 (1.9%)
Decreased appetite	1 (1.9%)	0
Diabetic metabolic decompensation	1 (1.9%)	0
Hypokalaemia	2 (3.8%)	0
Musculoskeletal and connective tissue disorders	2 (3.8%)	1 (1.9%)
Arthralgia	0	1 (1.9%)
Back pain	1 (1.9%)	0
Osteitis	1 (1.9%)	0
General disorders and administration site conditions	2 (3.8%)	1 (1.9%)
Oedema peripheral	1 (1.9%)	0
Pain	0	1 (1.9%)
General physical health deterioration	1 (1.9%)	0
Cardiac disorders	2 (3.8%)	2 (3.8%)
Angina pectoris	0	1 (1.9%)
Cardiac arrest	0	1 (1.9%) [1]
Acute myocardial infarction	1 (1.9%)	0
Cardiac failure	1 (1.9%)	0
Vascular disorders	1 (1.9%)	1 (1.9%)
Hypotension	0	1 (1.9%)
Extremity necrosis	1 (1.9%)	0
Respiratory, thoracic and mediastinal disorders [2]	0	1 (1.9%)
Pulmonary embolism	0	1 (1.9%)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Gastrointestinal disorders	0	1 (1.9%)
Haemorrhoids	0	1 (1.9%)
Hepatobiliary disorders	0	1 (1.9%)
Drug-induced liver injury	0	1 (1.9%)
Skin and subcutaneous tissue disorders	2 (3.8%)	0
Pemphigoid	2 (3.8%)	0
Investigations	2 (3.8%)	0
Blood pressure increased	1 (1.9%)	0
Weight decreased	1 (1.9%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.8%)	0
Basal cell carcinoma	1 (1.9%)	0
Oropharyngeal cancer	1 (1.9%)	0
Nervous system disorders	1 (1.9%)	0
Axonal neuropathy	1 (1.9%)	0
Renal and urinary disorders	1 (1.9%)	0
Acute kidney injury	1 (1.9%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SAE=serious adverse event; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
MedDRA (Version 27.1) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
[1] One event in the dupilumab 300 mg Q2W group (Cardiac arrest) occurred before the primary analysis data cutoff date. This event was considered as not treatment-emergent at that time, because it occurred 2 days after the end-of-study date. As of the CSR addendum database lock date, the end-of-study visit date for this participant was updated to occur approximately 2 months later, which resulted in re-classification of the event as treatment-emergent occurring during the on-treatment period through week 52.
[2] In the primary analysis, the Respiratory failure event in 1 participant in the placebo group was considered to have an onset during the on-treatment period. Since the primary analysis, the start month of the SAE leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52 as stated in the Primary Analysis CSR Amendment 1. As such, the event is no longer included in event counts during the on-treatment period through week 52.

Treatment-Related Treatment-Emergent Adverse Events

The proportion of participants who had at least 1 treatment-related TEAE (relatedness assessed by the investigator) during the on-treatment period through week 52 is shown in the Table 42 below.

The treatment-related TEAEs reported for more than 1 participant (regardless of treatment group) were Conjunctivitis (placebo: n=0; dupilumab 300 mg Q2W: n=2), Muscle spasms (placebo: n=1; dupilumab 300 mg Q2W: n=1), and Dry eye (placebo: n=2; dupilumab 300 mg Q2W: n=0). All treatment-related TEAEs were assessed by the investigators as mild or moderate in severity and non-serious. The only treatment-related event leading to study drug discontinuation was an event of Acute generalised exanthematous pustulosis in a participant in the dupilumab 300 mg Q2W group, see Adverse Events of Special Interest below.

Table 42. Summary of Treatment-Related TEAEs During the On-Treatment Period Through Week 52 up to Data Cutoff by Primary SOC and PT in Study R668-BP-1902 (SAF)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of participants with at least 1 treatment-related TEAE	8 (15.1%)	14 (26.4%)
Infections and infestations	2 (3.8%)	7 (13.2%)
Conjunctivitis	0	2 (3.8%)
Folliculitis	0	1 (1.9%)
Nasopharyngitis	0	1 (1.9%)
Oral herpes	0	1 (1.9%)
Upper respiratory tract infection	0	1 (1.9%)
Urinary tract infection	0	1 (1.9%)
Cellulitis	1 (1.9%)	0
Fungal foot infection	1 (1.9%)	0
Respiratory tract infection	1 (1.9%)	0
Skin and subcutaneous tissue disorders	3 (5.7%)	4 (7.5%)
Acute generalised exanthematous pustulosis	0	1 (1.9%)
Hyperhidrosis	0	1 (1.9%)
Onychoclasis	0	1 (1.9%)
Symmetrical drug-related intertriginous and flexural exanthema	0	1 (1.9%)
Intertrigo	1 (1.9%)	0
Pruritus	1 (1.9%)	0
Purpura	1 (1.9%)	0
Rash papular	1 (1.9%)	0
Blood and lymphatic system disorders	0	2 (3.8%)
Anaemia	0	1 (1.9%)
Eosinophilia	0	1 (1.9%)
Eye disorders	2 (3.8%)	2 (3.8%)
Keratitis	0	1 (1.9%)
Vision blurred	0	1 (1.9%)
Dry eye	2 (3.8%)	0
General disorders and administration site conditions	1 (1.9%)	2 (3.8%)
Injection site bruising	0	1 (1.9%)
Injection site erythema	0	1 (1.9%)
Injection site swelling	0	1 (1.9%)
Mucosal dryness	0	1 (1.9%)
Oedema peripheral	1 (1.9%)	0
Pain	1 (1.9%)	0
Gastrointestinal disorders	1 (1.9%)	1 (1.9%)
Flatulence	0	1 (1.9%)
Abdominal pain upper	1 (1.9%)	0
Dyspepsia	1 (1.9%)	0
Investigations	0	1 (1.9%)
Crystal urine present	0	1 (1.9%)

Metabolism and nutrition disorders	0	1 (1.9%)
Hypercholesterolaemia	0	1 (1.9%)
Musculoskeletal and connective tissue disorders	1 (1.9%)	1 (1.9%)
Muscle spasms	1 (1.9%)	1 (1.9%)
Renal and urinary disorders	0	1 (1.9%)
Haematuria	0	1 (1.9%)
Vascular disorders	1 (1.9%)	1 (1.9%)
Hypertension	0	1 (1.9%)
Vasculitis	1 (1.9%)	0
Nervous system disorders	2 (3.8%)	0
Dizziness	1 (1.9%)	0
Paraesthesia	1 (1.9%)	0
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0
Dyspnoea	1 (1.9%)	0

MedDRA (Version 27.0) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.3.2.4.b

Serious adverse event/deaths/other significant events

Deaths

A total of 8 participants had events with a fatal outcome in the study. During the on-treatment period, in the dupilumab 300 mg Q2W group, no study participants died following a TEAE; there was no change since the primary analysis. After the end of the on-treatment period, 2 participants experienced fatal outcome events. In the placebo group, 6/53 participants had a fatal outcome-TEAE through week 36, and 1 additional participant experienced fatal TEAE through week 52 (Table 43). All reported events were considered by the investigator to be unrelated to study drug

Dupilumab 300 mg Q2W group:

<u>After on-treatment period:</u>

– 1 participant (69-year-old female) had a fatal-outcome TE-SAE of Cardiac failure on day 413 and died the same day, in the follow-up period (the last dose of study drug was on day 357). The participant died in their sleep with cause of death reported as suspected heart failure. The participant did not report any symptoms prior to the event. Ongoing TEAEs at the time of death included mild Atrial fibrillation (onset study day 113) and mild Depression (onset study day 134). Relevant medical history included asthma, back pain, cataract, cystitis, nasal polyps, diabetes mellitus, hypertension, hepatic steatosis, and chronic kidney disease.

– 1 participant (72-year-old female) had a fatal-outcome SAE of Cardiogenic shock (post-CABG surgery) on day 217 with the AE onset after the end of study and died on day 222 (the last dose of study drug was on day 155 and the end-of-study visit was on day 207). The participant experienced a TE-SAE of Angina pectoris on study day 162 and was admitted to hospital on study day 167. Treatment for the TE-SAE (started study day 181) included cardiopulmonary bypass, CABG (complicated by on pump arrest), and coronary endarterectomy. The participant also received a percutaneous coronary intervention with stenting. The event of Angina pectoris was considered not

related to study drug but did result in study drug discontinuation. On study day 217, the participant experienced severe cardiogenic shock post CABG that led to a fatal outcome. Relevant concurrent conditions included: diabetes mellitus and hypertension.

Table 43. Summary of Deaths in Study R668-BP-1902 (SAF)

PRIMARY CAUSE OF DEATH/ PT of TEAE with Fatal Outcome	TEAE (Y/N)	Day of Last Dose of Study Drug	Study Period/Day of TEAE Onset	Study Period/Day of Death	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of deaths					5 (9.4%)	2 (3.8%)
LUNG FAILURE/ Respiratory failure	Y	268	On-treatment/ UNK [1]	Follow-up/382	1 (1.9%)	0
RAPID DETERIORATION OF GENERAL CONDITION/ General physical health deterioration	Y	1	On-treatment/1	After EOS/33	1 (1.9%)	0
MASSIVE CARDIAC EVENT/ Cardiovascular disorder	Y	57	Follow-up/77	Follow-up/77	1 (1.9%)	0
CRYPTOCOCCAL MENINGITIS/ Meningitis cryptococcal	Y	264	Follow-up/287	After EOS/289	1 (1.9%)	0
NATURAL CAUSES / Death	Y	365	Follow-up/424	Follow-up/424	1 (1.9%)	0
SUSPECTED HEART FAILURE/ Cardiac failure	Y	357	Follow-up/413	Follow-up/413	0	1 (1.9%)
CARDIOGENIC SHOCK(POST-SURGICAL CABG) / Cardiogenic shock	N	155	After EOS/217	After EOS/222	0	1 (1.9%)

Table includes all deaths, regardless of timing, up to database lock.
The on-treatment period through week 52 is the time from the administration of the first dose of study drug to the date of the last dose of study drug +14 days.
The follow-up period is the time from the day after the end of the on-treatment period to the end of study date.
[1] Exact event start date was unknown.
Abbreviations: CABG=coronary artery bypass grafting; EOS=end of study; N=no; PT=preferred term; Q2W=every 2 weeks; SAF=safety analysis set; TEAE=treatment-emergent adverse event; UNK=unknown; Y=yes.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.3.3.1, PTL 16.2.1.1, PTL 16.2.7.3

Placebo group:

<u>On-treatment period:</u>

- 1 participant in the placebo group had a fatal TE-SAE (PT: General physical health deterioration) with an onset occurring during the on-treatment period through week 52. In the primary analysis, 2 participants were reported with fatal SAEs during the on-treatment period through week 52 in the placebo group. However, in the final analysis, the number of participants with fatal SAEs during the on-treatment period through week 52 decreased to 1 participant as follow-up information was received for 1 participant in the placebo group who died due to Respiratory failure. In the Primary Analysis CSR Amendment 1, the fatal, severe SAE of Respiratory failure was considered to have an onset during the on-treatment period. Since the primary analysis, upon receipt of the follow-up information, the start month of the SAE leading to death was updated (Post-text Listing 16.2.7.3.B). Due to the update, the fatal event onset is now considered to have occurred during the post-treatment follow-up period. As

such, the event is no longer included in event counts during the on-treatment period through week 52.

After on-treatment period:

- 4 participants in the placebo group had fatal TE-SAEs with an onset during the post-treatment follow-up period: Respiratory failure, Cardiovascular disorder (VT: death [massive cardiovascular event]), Meningitis cryptococcal, and Death from natural causes.
- 1 participant in the placebo group had a fatal SAE of Small cell lung cancer metastatic (new event reported since the primary analysis) with an onset after the end of study.

Table 44. Summary of Deaths (SAF)

PRIMARY CAUSE OF DEATH/ PT of TEAE with Fatal Outcome	TEAE (Y/N)	Day of Last Dose of Study Drug	Study Period/Day of TEAE Onset	Study Period/Day of Death	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of deaths					6 (11.3%)	2 (3.8%)
RAPID DETERIORATION OF GENERAL CONDITION/ General physical health deterioration	Y	1	On-treatment/ 1	After EOS/33	1 (1.9%)	0
LUNG FAILURE/ Respiratory failure	Y	268	Follow-up / UNK [1]	Follow-up/382	1 (1.9%)	0
MASSIVE CARDIAC EVENT/ Cardiovascular disorder	Y	57	Follow-up/77	Follow-up/77	1 (1.9%)	0
CRYPTOCOCCAL MENINGITIS/ Meningitis cryptococcal	Y	264	Follow-up/287	After EOS/289	1 (1.9%)	0
NATURAL CAUSES / Death	Y	365	Follow-up/424	Follow-up/424	1 (1.9%)	0
SUSPECTED HEART FAILURE/ Cardiac failure	Y	357	Follow-up/413	Follow-up/413	0	1 (1.9%)
CARDIOGENIC SHOCK (POST-SURGICAL CABG) / Cardiogenic shock	N	155	After EOS/217	After EOS/222	0	1 (1.9%)
METASTATIC SMALL CELL LUNGCANCER/ Small cell lung cancer metastatic	N	351	After EOS/455	After EOS/531	1 (1.9%)	0

Abbreviations: CABG=coronary artery bypass grafting; EOS=end of study; N=no; PT=preferred term; Q2W=every 2 weeks; SAE=safety analysis set; SAF=safety analysis set; TEAE=treatment-emergent adverse event; UNK=unknown; Y=yes.
The on-treatment period through week 52 is the time from the administration of the first dose of study drug to the date of the last dose of study drug +14 days.
The follow-up period is the time from the day after the end of the on-treatment period to the end of study date.
[1] Exact event start date was unknown. Since the Primary Analysis CSR Amendment 1 cutoff date, follow-up information was received for this participant and the start month of the SAE (Respiratory failure) leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52 as stated in the Primary Analysis CSR Amendment 1.

Other Serious Adverse Events

Treatment-Emergent Serious Adverse Events

The number of participants with TE-SAE during the on-treatment period through week 52 is presented in the Table 45 below. Respective exposure-adjusted incidence rates of TE-SAEs are shown in the Table 45 below.

Table 45. Number of Participants with Treatment-Emergent Serious Adverse Events During the On-Treatment Period Through Week 52 by Primary SOC and PT (SAF)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of participants with at least 1 TE-SAE	16 (30.2%)	12 (22.6%)
Infections and infestations	4 (7.5%)	4 (7.5%)
Pneumonia	0	2 (3.8%)
Arthritis bacterial	0	1 (1.9%)
Post procedural infection	0	1 (1.9%)
Urosepsis	0	1 (1.9%)
COVID-19	1 (1.9%)	0
Cellulitis	2 (3.8%)	0
Urinary tract infection	1 (1.9%)	0
Injury, poisoning and procedural complications	3 (5.7%)	3 (5.7%)
Depressed fracture	0	1 (1.9%)
Fall	0	1 (1.9%)
Spinal fracture	0	1 (1.9%)
Craniofacial fracture	1 (1.9%)	0
Joint injury	1 (1.9%)	0
Procedural pain	1 (1.9%)	0
Upper limb fracture	1 (1.9%)	0
Cardiac disorders	2 (3.8%)	2 (3.8%)
Angina pectoris	0	1 (1.9%)
Cardiac arrest [1]	0	1 (1.9%)
Acute myocardial infarction	1 (1.9%)	0
Cardiac failure	1 (1.9%)	0
Renal and urinary disorders	0	2 (3.8%)
Nephrolithiasis	0	1 (1.9%)
Renal failure	0	1 (1.9%)
Gastrointestinal disorders	1 (1.9%)	1 (1.9%)
Haemorrhoids	0	1 (1.9%)
Inguinal hernia	1 (1.9%)	0
Metabolism and nutrition disorders	3 (5.7%)	1 (1.9%)
Diabetes mellitus	0	1 (1.9%)
Decreased appetite	1 (1.9%)	0
Diabetic metabolic decompensation	1 (1.9%)	0
Hyperglycaemia	1 (1.9%)	0
Hypokalaemia	1 (1.9%)	0
Reproductive system and breast disorders	0	1 (1.9%)
Postmenopausal haemorrhage	0	1 (1.9%)
Respiratory, thoracic and mediastinal disorders [2]	1 (1.9%)	1 (1.9%)
Pulmonary embolism	0	1 (1.9%)
Pulmonary cavitation	1 (1.9%)	0
Vascular disorders	1 (1.9%)	1 (1.9%)

Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Circulatory collapse	0	1 (1.9%)
Extremity necrosis	1 (1.9%)	0
Eye disorders	1 (1.9%)	0
Cataract	1 (1.9%)	0
Glaucoma	1 (1.9%)	0
General disorders and administration site conditions	1 (1.9%)	0
General physical health deterioration	1 (1.9%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (5.7%)	0
Basal cell carcinoma	1 (1.9%)	0
Oropharyngeal cancer	1 (1.9%)	0
Prostate cancer	1 (1.9%)	0
Nervous system disorders	2 (3.8%)	0
Axonal neuropathy	1 (1.9%)	0
Transient ischaemic attack	1 (1.9%)	0
Skin and subcutaneous tissue disorders	2 (3.8%)	0
Pemphigoid	2 (3.8%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SAE=serious adverse event; SAF=safety analysis set; SOC=system organ class; TE =treatment-emergent.
MedDRA (Version 27.1) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
[1] One event in the dupilumab 300 mg Q2W group (Cardiac arrest) occurred before the Primary Analysis CSR Amendment 1 cutoff date. This event was considered as not treatment-emergent at that time, because it occurred 2 days after the end-of-study visit date. As of the CSR addendum database lock date, the end-of-study visit date for this participant was updated to occur approximately 2 months later, which resulted in re-classification of the event as treatment-emergent during the on-treatment period through week 52.
[2] Since the Primary Analysis CSR Amendment 1 cutoff date, follow-up information was received for 1 participant in the placebo group and the start month of the SAE (Respiratory failure) leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52 as stated in the Primary Analysis CSR Amendment 1.

Table 46. Number of Participants (per 100 Participant-Years) with Treatment-Emergent Serious Adverse Events During the On-Treatment Period Through Week 52 by Primary SOC and PT (SAF)

Primary System Organ Class Preferred Term	Placebo (N=53) nP/PY (nP/100 PY)	Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)
Participants with at least 1 TE-SAE	16/35.1 (45.62)	12/39.8 (30.12)
Infections and infestations	4/38.2 (10.46)	4/44.8 (8.92)
Pneumonia	0/39.8 (0.00)	2/46.0 (4.35)
Arthritis bacterial	0/39.8 (0.00)	1/45.5 (2.20)
Post procedural infection	0/39.8 (0.00)	1/46.1 (2.17)
Urosepsis	0/39.8 (0.00)	1/46.5 (2.15)
COVID-19	1/39.8 (2.51)	0/46.6 (0.00)
Cellulitis	2/39.1 (5.11)	0/46.6 (0.00)
Urinary tract infection	1/39.0 (2.57)	0/46.6 (0.00)

Primary System Organ Class Preferred Term	Placebo (N=53) nP/PY (nP/100 PY)	Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)
Injury, poisoning and procedural complications	3/38.4 (7.81)	3/44.9 (6.68)
Fall	0/39.8 (0.00)	1/45.7 (2.19)
Spinal fracture	0/39.8 (0.00)	1/45.9 (2.18)
Depressed fracture	0/39.8 (0.00)	1/46.5 (2.15)
Craniofacial fracture	1/38.9 (2.57)	0/46.6 (0.00)
Joint injury	1/39.8 (2.51)	0/46.6 (0.00)
Procedural pain	1/39.3 (2.54)	0/46.6 (0.00)
Upper limb fracture	1/39.8 (2.51)	0/46.6 (0.00)
Renal and urinary disorders	0/39.8 (0.00)	2/46.0 (4.35)
Renal failure	0/39.8 (0.00)	1/46.0 (2.17)
Nephrolithiasis	0/39.8 (0.00)	1/46.5 (2.15)
Cardiac disorders	2/39.7 (5.03)	2/46.5 (4.30)
Cardiac arrest [1]	0/39.8 (0.00)	1/46.5 (2.15)
Angina pectoris	0/39.8 (0.00)	1/46.6 (2.15)
Acute myocardial infarction	1/39.8 (2.51)	0/46.6 (0.00)
Cardiac failure	1/39.8 (2.51)	0/46.6 (0.00)
Gastrointestinal disorders	1/39.4 (2.54)	1/45.5 (2.20)
Haemorrhoids	0/39.8 (0.00)	1/45.5 (2.20)
Inguinal hernia	1/39.4 (2.54)	0/46.6 (0.00)
Metabolism and nutrition disorders	3/39.2 (7.65)	1/45.6 (2.19)
Diabetes mellitus	0/39.8 (0.00)	1/45.6 (2.19)
Decreased appetite	1/39.8 (2.51)	0/46.6 (0.00)
Diabetic metabolic decompensation	1/39.6 (2.53)	0/46.6 (0.00)
Hyperglycaemia	1/39.5 (2.53)	0/46.6 (0.00)
Hypokalaemia	1/39.7 (2.52)	0/46.6 (0.00)
Vascular disorders	1/39.6 (2.53)	1/45.8 (2.19)
Circulatory collapse	0/39.8 (0.00)	1/45.8 (2.19)
Extremity necrosis	1/39.6 (2.53)	0/46.6 (0.00)
Respiratory, thoracic and mediastinal disorders [2]	1/39.8 (2.51)	1/45.8 (2.18)
Pulmonary embolism	0/39.8 (0.00)	1/45.8 (2.18)
Pulmonary cavitation	1/39.8 (2.51)	0/46.6 (0.00)
Reproductive system and breast disorders	0/39.8 (0.00)	1/46.3 (2.16)
Postmenopausal haemorrhage	0/39.8 (0.00)	1/46.3 (2.16)
Eye disorders	1/39.7 (2.52)	0/46.6 (0.00)
Cataract	1/39.7 (2.52)	0/46.6 (0.00)
Glaucoma	1/39.7 (2.52)	0/46.6 (0.00)
General disorders and administration site conditions	1/39.8 (2.51)	0/46.6 (0.00)
General physical health deterioration	1/39.8 (2.51)	0/46.6 (0.00)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3/39.8 (7.55)	0/46.6 (0.00)
Basal cell carcinoma	1/39.8 (2.51)	0/46.6 (0.00)

Primary System Organ Class Preferred Term	Placebo (N=53) nP/PY (nP/100 PY)	Dupilumab 300 mg Q2W (N=53) nP/PY (nP/100 PY)
Oropharyngeal cancer	1/39.8 (2.51)	0/46.6 (0.00)
Prostate cancer	1/39.8 (2.51)	0/46.6 (0.00)
Nervous system disorders	2/39.3 (5.09)	0/46.6 (0.00)
Axonal neuropathy	1/39.6 (2.53)	0/46.6 (0.00)
Transient ischaemic attack	1/39.6 (2.53)	0/46.6 (0.00)
Skin and subcutaneous tissue disorders	2/38.9 (5.14)	0/46.6 (0.00)
Pemphigoid	2/38.9 (5.14)	0/46.6 (0.00)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; nP=number of participants with an event; nP/100 PY=number of participants with at least one event per 100 participant-years; PT=preferred term; PY=participant-years; Q2W=every 2 weeks; SAE=serious adverse event; SAF=safety analysis set; SOC=system organ class; TE =treatment-emergent.
For participants with the given event, the number of participant-years is calculated up to the date of the first such event; for participants without the given event, the number of participant-years corresponds to the length of the treatment period.
MedDRA (Version 27.1) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing incidence per 100 participant-years at all levels in the dupilumab 300 mg Q2W group.
[1] One event in the dupilumab 300 mg Q2W group (Cardiac arrest) occurred before the Primary Analysis CSR Amendment 1 cutoff date. This event was considered as not treatment-emergent at that time, because it occurred 2 days after the end-of-study visit date. As of the CSR addendum database lock date, the end-of-study visit date for this participant was updated to occur approximately 2 months later, which resulted in re-classification of the event as treatment-emergent during the on-treatment period through week 52.
[2] Since the Primary Analysis CSR Amendment 1 cutoff date, follow-up information was received for 1 participant in the placebo group and the start month of the SAE (Respiratory failure) leading to death was updated. Due to the update, the SAE was determined to have occurred during the follow-up period and not during the on-treatment period through week 52 as stated in the Primary Analysis CSR Amendment 1.

Adverse Events of Special Interest

A summary of TE-AESIs during the on-treatment period through week 52 is provided in the Table 47 below.

Table 47. Overall Summary of Number of Participants with Treatment-Emergent AESIs During the On-Treatment Period Through Week 52 up to Data Cutoff by Primary SOC and PT (SAF)

AESI Category Primary System Organ Class Preferred Term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of participants with at least 1 TE AESI	0	4 (7.5%)
Keratitis	0	2 (3.8%)
Eye disorders	0	2 (3.8%)
Keratitis	0	2 (3.8%)
Anaphylactic reactions	0	1 (1.9%)
Vascular disorders	0	1 (1.9%)
Circulatory collapse	0	1 (1.9%)
Systemic hypersensitivity reactions	0	1 (1.9%)
Skin and subcutaneous tissue disorders	0	1 (1.9%)
Acute generalised exanthematous pustulosis	0	1 (1.9%)

MedDRA (Version 27.0) coding dictionary applied. At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SOC=system organ class; TE=treatment-emergent.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.3.3.6.b

In total, 4 participants in the dupilumab 300 mg Q2W group, and 0 participants in the placebo group, had TE-AESIs during the on-treatment period through week 52 up to data cutoff:

• 1 participant experienced 2 events of Keratitis. The first event of Keratitis was recorded from study day 89 to 95. The investigator attributed this event of mild Keratitis to a foreign object (nylon cord) found in the participant's eye. The first event of Keratitis was treated with ophthalmic ciprofloxacin hydrochloride, ophthalmic tobramycin, and ophthalmic hyaluronate sodium. The second event of Keratitis, which was moderate in severity, began on study day 157 and was ongoing at data cutoff. The second event of Keratitis was treated with ophthalmic hyaluronate sodium and ophthalmic light liquid araffin/paraffin, liquid/petrolatum/retinol palmitate/wool fat. The investigator considered the **second event of Keratitis as related** to study drug. Neither of the events resulted in study drug discontinuation.

• 1 additional participant experienced an event of mild Keratitis which was considered **unrelated** to study drug by the investigator. The event was recorded from study day 271 and was considered to be resolving at the time of the data cutoff. No treatment was recorded for the event of Keratitis. The participant also experienced non-serious TEAEs of Conjunctival haemorrhage (study day 92 to 110) and Eye paraesthesia (study day 109 to 278); both events were assessed by the investigator as moderate in severity **and not related** to study drug.

• 1 participant had an AESI identified in the category of anaphylactic reactions. The participant experienced an event of moderate Circulatory collapse from study day 69 to 71. Per the investigator, the AESI of Circulatory collapse was due to an overdose of ramipril; although this TE-SAE is presented as an AESI per the anaphylactic reaction search algorithm, the investigator did **not consider the event an AESI of anaphylactic reaction nor related to study drug.**

• 1 participant had an AESI reported in the category of systemic hypersensitivity reactions. The participant experienced an event of moderate Acute generalised exanthematous pustulosis. On an

unspecified date, the participant started to experience new lesions with few pustules and desquamation on erythematous plaque on the right lower leg. On study day 101, the participant experienced a non-serious AE of mild Skin exfoliation (verbatim: desquamation left leg). On study day 109, the participant reported weakness and tiredness and presented with noticeable increase in the number of plaques on the whole integument. AGEP was diagnosed via biopsy (differential diagnosis included pustular psoriasis) on study day 114. On the same day, blood tests showed increased neutrophils and platelets. There was no fever or mucosal involvement. The event led to permanent discontinuation of study drug and the study. The investigator assessed the event to be **related** to study drug. The participant received lobetasol propionate daily topically (dose unspecified) and prednisolone 30 mg daily orally; after 1 week, there was mild improvement of the disease. At the time of study discontinuation, the event was considered resolving. AGEP is a cutaneous reaction primarily associated with medication use, particularly antibiotics. However, AGEP can also be triggered by other factors, including viral, bacterial, and parasitic infections, as well as herbal medications. The latency period between exposure and onset of AGEP is typically short, with most cases appearing within 1 to 5 days of initiating a new medication. While the reaction can manifest up to 10 days post-exposure, it is rare for AGEP to occur beyond this timeframe. The temporal relationship is a crucial factor in assessing potential causality in suspected AGEP cases. In this case, the event of AGEP started on study day 109, after the participant had received 8 doses of dupilumab 300 mg Q2W. No AESIs of helminthic infection, severe conjunctivitis or blepharitis, or clinically symptomatic eosinophilia were reported.

Analysis of Adverse Events by Organ System or Syndrome

AEs in the following MedDRA SOCs were selected for evaluation based on their potential relevance to BP and associated comorbidities, dupilumab, or their incidence in the study population: Infections and infestations, Nervous system disorders, Metabolism and nutrition disorders, Vascular disorders, Cardiac disorders.

Infections and infestations

The proportion of participants with TEAEs in this SOC during the on-treatment period through week 52 up to data cutoff was similar between the placebo group (50.9%; 27/53) and the dupilumab 300 mg Q2W group (52.8%; 28/53). The TEAEs reported in ≥5% of participants in either treatment group were:

- Nasopharyngitis (placebo: 15.1% [8/53]; dupilumab 300 mg Q2W: 13.2% [7/53])
- COVID-19 (placebo: 5.7% [3/53]; dupilumab 300 mg Q2W: 5.7% [3/53])
- Oral candidiasis (placebo: 5.7% [3/53]; dupilumab 300 mg Q2W: 3.8% [2/53])
- Cellulitis (placebo: 5.7% [3/53]; dupilumab 300 mg Q2W: 0% [0/53])
- Gastroenteritis (placebo: 5.7% [3/53]; dupilumab 300 mg Q2W: 0% [0/53])
- Upper respiratory tract infection (placebo: 1.9% [1/53]; dupilumab 300 mg Q2W: 5.7% [3/53])
- Conjunctivitis (placebo: 0% [0/53]; dupilumab 300 mg Q2W: 7.5% [4/53])

Severe TEAEs in this SOC were reported in 4 participants in the placebo group (each in 1 participant: COVID-19, Urinary tract infection, Cellulitis, Erysipelas) and 3 participants in the dupilumab 300 mg Q2W group (Arthritis bacterial and Post procedural infection in 1 participant; Pneumonia in 1 participant; Urosepsis in 1 participant); the events in these participants were also assessed by the investigator as serious. One additional TE-SAE of Pneumonia, which was not assessed to be severe, was reported in another participant in the dupilumab 300 mg Q2W group. TEAEs in this SOC leading to study drug discontinuation were reported in 1 participant in the placebo group (COVID-19) and 0

participants in the dupilumab 300 mg Q2W group. 1 participant in the placebo group and 0 participants in the dupilumab 300 mg Q2W group had a TEAE with a fatal outcome in the SOC of Infections and infestations up to the time of database lock. The fatal event was treatment-emergent, but with an onset during the follow-up period, so it is not included in the summaries of the on-treatment period through week 52 up to data cutoff. The participant in the placebo group had a TE-SAE of Meningitis cryptococcal with the AE onset in the follow-up period on day 287 (the last dose of study drug was on day 264) and died on day 289, after the end of study on day 288.

Nervous system disorders

The proportion of participants with TEAEs in this SOC during the on-treatment period through week 52 up to data cutoff was similar between the placebo group (26.4%; 14/53) and the dupilumab 300 mg Q2W group (24.5%; 13/53). The only TEAE reported in ≥5% of participants in either treatment group was Headache (placebo: 9.4% [5/53]; dupilumab 300 mg Q2W: 7.5% [4/53]). Severe TEAEs in this SOC were reported in 1 participant in the placebo group (Axonal neuropathy) and 0 participants in the dupilumab 300 mg Q2W group. TE-SAEs in this SOC were reported in 2 participants in the placebo group (Axonal neuropathy and Transient ischaemic attack) and 0 participants in the dupilumab 300 mg Q2W group. No TEAEs in this SOC led to study drug discontinuation. No participants had a TEAE with a fatal outcome in the SOC of Nervous system disorders up to the time of database lock.

Metabolism and nutrition disorders

The proportion of participants with TEAEs in this SOC during the on-treatment period through week 52 up to data cutoff was similar between the placebo group (24.5%; 13/53) and the dupilumab 300 mg Q2W group (22.6%; 12/53).

The TEAEs reported in ≥5% of participants in either treatment group were:

- Hyperglycaemia (placebo: 7.5% [4/53]; dupilumab 300 mg Q2W: 1.9% [1/53])
- Decreased appetite (placebo: 7.5% [4/53]; dupilumab 300 mg Q2W: 0% [0/53])

Severe TEAEs in this SOC were reported in 3 participants in the placebo group (Diabetic metabolic decompensation and Hypokalaemia in 1 participant; Decreased appetite and Hypokalaemia in 1 participant; Hyperglycaemia in 1 participant) and 1 participant in the dupilumab 300 mg Q2W group (Hypernatraemia). TE-SAEs in this SOC were reported in 3 participants in the placebo group and 1 participant in the dupilumab 300 mg Q2W group (Diabetes mellitus). In the placebo group, the severe TEAEs of Diabetic metabolic decompensation and Hypokalaemia in 1 participant and Decreased appetite in 1 participant were also assessed by the investigator to be serious; a separate participant experienced a non-severe TESAE of Hyperglycaemia. No TEAEs in this SOC led to study drug discontinuation. No participants had a TEAE with a fatal outcome in the SOC of Metabolism and nutrition disorders up to the time of database lock.

Vascular disorders

The proportion of participants with TEAEs in this SOC during the on-treatment period through week 52 up to data cutoff was similar between the placebo group (17.0%; 9/53) and the dupilumab 300 mg Q2W group (18.9%; 10/53). The only TEAE reported in ≥5% of participants in either treatment group was Hypertension (placebo: 5.7% [3/53]; dupilumab 300 mg Q2W: 7.5% [4/53]). Severe TEAEs in this SOC were reported in 1 participant in each treatment group (Extremity necrosis in the placebo group and Hypotension in the dupilumab 300 mg Q2W group). TE-SAEs in this SOC were reported in 1 participant in each treatment group (Extremity necrosis in the placebo group and Circulatory collapse in the dupilumab 300 mg Q2W group). Per the investigator, the TE-SAE of Circulatory collapse was due

to an overdose of ramipril. No TEAEs in this SOC led to study drug discontinuation. No participants had a TEAE with a fatal outcome in the SOC of Vascular disorders up to the time of database lock.

Cardiac disorders

The proportion of participants with TEAEs in this SOC during the on-treatment period through week 52 up to data cutoff was similar between the placebo group (9.4%; 5/53) and the dupilumab 300 mg Q2W group (11.3%; 6/53). In each treatment group, the only TEAE reported in >1 participant was Cardiac failure (2 participants in the placebo group). All other TEAEs were reported for a single participant in each treatment group (in the placebo group: Atrial fibrillation, Acute myocardial infarction, Coronary artery disease, Tachycardia; in the dupilumab 300 mg Q2W group: Angina pectoris, Atrial fibrillation, Cardiac failure congestive, Myocardial ischaemia, Palpitations, Pericardial effusion, Ventricular tachycardia). No TEAEs in the SOC of Cardiac disorders were considered related to study drug by the investigators. Severe TEAEs in this SOC were reported in 2 participants in the placebo group (Acute myocardial infarction and Cardiac failure) and 2 participants in the dupilumab 300 mg Q2W group; the events in these 4 participants were also assessed to be serious. The events of Angina pectoris and Cardiac arrest in the dupilumab 300 mg Q2W group also led to study drug discontinuation. The TEAE of Cardiac arrest, which occurred post-colonoscopy/endoscopy procedure, in the dupilumab 300 mg Q2W group was erroneously not captured as during the on-treatment period; further details, including a mini-narrative of this event, are provided in Section 2.1.5.1. There were no TEAEs in this SOC leading to study drug discontinuation in the placebo group during the ontreatment period through week 52 up to data cutoff.

1 participant in the placebo group and 2 participants in the dupilumab 300 mg Q2W group had fatal AEs in the SOC of Cardiac disorders up to the time of database lock:

• 1 participant in the placebo group had a TE-SAE of Cardiovascular disorder with the AE onset on day 77 and died the same day, in the follow-up period (the last dose of study drug was on day 57).

• 1 participant in the dupilumab 300 mg Q2W group had a TE-SAE of Cardiac failure on day 413 and died the same day, in the follow-up period (the last dose of study drug was on day 357).

• 1 participant in the dupilumab 300 mg Q2W group had an SAE of Cardiogenic shock (post-CABG surgery) on day 217 with the AE onset after the end of study and died on day 222 (the last dose of study drug was on day 155 and the end-of-study visit was on day 207).

All AEs with a fatal outcome were considered by the investigator to be unrelated to study drug.

Cardiovascular thromboembolic events were identified via blinded adjudication by the study medical monitor of all AEs with a PT within the following SMQs with narrow scope: Arrhythmia related investigations, signs and symptoms, Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias), Congenital and neonatal arrhythmias, Cardiac failure, Cardiomyopathy, Central nervous system haemorrhages and cerebrovascular conditions, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic, Convulsions, Embolic and thrombotic events, arterial, Myocardial infarction, Other ischaemic heart disease, Pulmonary hypertension, and Shock-associated circulatory or cardiac conditions (excl torsade de pointes).

During the on-treatment period through week 52 up to data cutoff, cardiovascular thromboembolic events were reported in 1 participant in the placebo group (PT: Acute myocardial infarction) and 0 participants in the dupilumab 300 mg Q2W group (Table 48). The TE-SAE of Acute myocardial infarction occurred on study day 187, 4 days after the participant discontinued study drug (reason: withdrawal of consent). The TE-SAE was assessed to be severe and not related to study drug and resolved on study day 192. A TE-SAE of Pulmonary embolism, which was not captured as part of the assessment above, was reported in a 62-year-old male participant in the dupilumab 300 mg Q2W

group, with relevant medical history of colitis ulcerative and hypertension. The event was assessed as severe and not related to study drug by the investigator. The event was considered by the investigator as more likely related to prednisone and to other hypercoagulable risk factors (sedentary lifestyle, smoking, or alcohol use) than the study drug. The event did not result in study drug discontinuation and resolved with medication.

Table 48. Number of Participants with Cardiovascular Thromboembolic Events During the On-Treatment Period Through Week 52 up to Data Cutoff in Study R668-BP-1902 (SAF)

Primary SOC Preferred term	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Number of participants with at least 1 cardiovascular thromboembolic event	1 (1.9%)	0
Cardiac disorders	1 (1.9%)	0
Acute myocardial infarction	1 (1.9%)	0

Cardiovascular thromboembolic events were identified via blinded adjudication by the study medical monitor of all adverse events with preferred term within the following SMQs with narrow scope: Arrhythmia related investigations, signs and symptoms, Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias), Congenital and neonatal arrhythmias, Cardiac failure, Cardiomyopathy, Central nervous system haemorrhages and cerebrovascular conditions, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic, Convulsions, Embolic and thrombotic events, arterial, Myocardial infarction, Other ischaemic heart disease, Pulmonary hypertension, and Shock-associated circulatory or cardiac conditions (excl torsade de pointes).
MedDRA (Version 27.0) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events. Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; Q2W=every 2 weeks; SAF=safety analysis set; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.3 PTT 14.3.3.11.b

Adverse Drug Reactions

ADRs are defined as undesirable effects that are reasonably associated with the use of a drug and which may occur as part of the pharmacological action of the drug or may be unpredictable in their occurrence. This definition does not include all TEAEs observed during the use of a drug, only those TEAEs for which there is a reasonable possibility of a causal relationship between the study drug and its occurrence.

ADRs were determined by a sequential process, initially by applying a threshold as the objective criteria, followed by a clinical assessment to determine if a reasonable relationship could be established. A TEAE that does not meet the threshold, or a cluster of PTs (identified based on medical concept consisting of similar medical terms [CMQ]), could also be identified for additional review based on clinical relevance.

To qualify as a potential ADR, any TEAE PT had to fulfill the following quantitative criteria:

• Incidence was ≥5% in the dupilumab 300 mg Q2W group with a ≥2% difference versus the placebo group, and

• The lower bound of the 95% CI for Cox hazard ratio of dupilumab 300 mg Q2W versus placebo was ≥1

The identified TEAEs were then further evaluated by medical judgment for potential inclusion as ADRs. In addition, selected AEs/AE grouping which have been previously established as ADRs for dupilumab in other approved indications (AD, Asthma, CRSwNP, EoE, PN, and COPD) were assessed for a numerical imbalance between groups. Less frequent PTs not fulfilling the initial quantitative criteria

were also evaluated to determine if any PT could qualify as an ADR based on pathobiological mechanisms or medical judgment. Medical review/clinical assessment for ADRs focused on the following considerations: 1) a plausible mechanism of action,

2) presence of confounders and/or alternative explanation, and

3) a plausible dose/exposure relationship.

When evaluating ADRs, it is important to account for the differences between the treatment groups in medical comorbidities, prior and ongoing treatment for both BP and comorbidities, and risks associated with polypharmacy in an elderly population enrolled in Study R668-BP-1902. None of the PTs met both of the quantitative ADR criteria mentioned above. The PTs or cluster of PTs with an incidence ≥5% in the dupilumab 300 mg Q2W group and a ≥2% difference versus the placebo group are summarized in Table 49 and further discussed below. For all events, the lower bound of the 95% CI for Cox hazard ratio of dupilumab 300 mg Q2W versus placebo was <1, therefore not demonstrating a nominally significant difference between dupilumab and placebo, or not computable.

Table 49. Number of Participants with TEAEs with an Incidence >5% in the Dupilumab 300 mg Q2W Group and a Difference ≥2% vs the Placebo Group by PT During the On-Treatment Period Through Week 52 up to Data Cutoff in Study R668-BP-1902 (SAF)

Primary System Organ Class Preferred term	Placebo (N=53) n (%)	Dupilumab 300 mg Q2W (N=53) n (%)	HR (95% CI)
Infections and infestations	27 (50.9%)	28 (52.8%)	0.94 (0.55, 1.59)
Conjunctivitis	0	4 (7.5%)	NC (NC, NC)
Upper respiratory tract infection	1 (1.9%)	3 (5.7%)	2.37 (0.25, 22.90)
Gastrointestinal disorders	17 (32.1%)	18 (34.0%)	1.00 (0.51, 1.94)
Constipation	1 (1.9%)	4 (7.5%)	3.80 (0.42, 34.09)
Musculoskeletal and connective tissue disorders	11 (20.8%)	17 (32.1%)	1.54 (0.72, 3.30)
Arthralgia	3 (5.7%)	5 (9.4%)	1.48 (0.35, 6.22)
Back pain	2 (3.8%)	4 (7.5%)	1.64 (0.30, 8.97)
General disorders and administration site conditions	13 (24.5%)	13 (24.5%)	0.94 (0.44, 2.03)
Oedema peripheral	5 (9.4%)	8 (15.1%)	1.47 (0.48, 4.50)
Eye disorders	8 (15.1%)	10 (18.9%)	1.15 (0.45, 2.91)
Vision blurred	0	4 (7.5%)	NC (NC, NC)
Respiratory, thoracic and mediastinal disorders	9 (17.0%)	9 (17.0%)	0.83 (0.33, 2.10)
Asthma	1 (1.9%)	4 (7.5%)	3.37 (0.38, 30.22)

MedDRA (Version 27.0) coding dictionary applied.
Participants without events were censored at the end of the treatment period.
HR and corresponding 95% CIs are based on a Cox proportional hazards model including treatment group as a covariate.
Sorted by decreasing frequency at all levels in the dupilumab 300 mg Q2W group.
Abbreviations: CI=confidence interval; HR=hazard ratio; MedDRA=Medical Dictionary for Regulatory Activities; NC=not computable; Q2W=every 2 weeks; SAF=safety analysis set; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTT 14.3.2.1.b and Module 5.3.5.3 PTT 14.3.3.20.b

The following PTs or cluster of PTs had an incidence ≥5% in the dupilumab 300 mg Q2W group and a ≥2% difference versus the placebo group:

Conjunctivitis is considered an ADR for dupilumab in patients with BP. Conjunctivitis has previously been identified as an ADR for the approved indications of AD, CRSwNP, and PN. Two conjunctivitis CMQs (narrow and broad) and a third conjunctivitis cluster (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Eye inflammation, Eye irritation, Giant papillary conjunctivitis) were used to search for similar medical concepts. Conjunctivitis was reported in 4 (7.5%) participants in the dupilumab 300 mg Q2W group and 0 participants in the placebo group; all reported events had the PT Conjunctivitis. At the PT level, the hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was not computable as no participants in the placebo group experienced Conjunctivitis. The time to onset ranged from 56 to 177 days post-study drug initiation. None of these TEAEs resulted in discontinuation of study drug. 2 of 4 events of Conjunctivitis were deemed by the investigator as related to dupilumab. 2 events resolved during the study period. None of the participants had recurring events of Conjunctivitis. None of the events were assessed by the investigator as serious or severe. Given that this is an established ADR for other dupilumab indications and with limited confounders in the reported cases, the event is considered an ADR for the BP indication.

Oedema peripheral is not considered an ADR for dupilumab in patients with BP. At the PT level, Oedema peripheral was reported in 8 (15.1%) participants in the dupilumab 300 mg Q2W group and 5 (9.4%) participants in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was 1.47 (0.48, 4.50).

• It is noteworthy that events similar to Oedema peripheral, specifically Peripheral swelling and Lymphoedema, were observed in the placebo group at a frequency of 1 participant each (1.9%). Conversely, no such events were reported in the dupilumab 300 mg Q2W group.

• Additionally, calcium channel blockers and chronic kidney disease are recognized risk factors for peripheral oedema, as they can disrupt fluid balance and promote fluid accumulation in the body's tissues. The baseline data indicate that the dupilumab 300 mg Q2W group had a higher proportion of participants already taking a calcium channel blocker (28.3% vs 17.0% in the placebo group) and a higher prevalence of chronic kidney disease (3 participants [5.7%] vs 0 in the placebo group). This suggests a potential pre-existing susceptibility to peripheral oedema in the dupilumab 300 mg Q2W group, even before the initiation of the study drug.

• No temporal association was observed in the occurrence of Oedema peripheral and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group was variable, ranging from 22 to 305 days after study drug initiation.

• None of these TEAEs resulted in permanent discontinuation of dupilumab and all events resolved while on study drug with the exception of 1 event reported in 1 participant who had already discontinued treatment.

• Except for 1 participant in the dupilumab 300 mg Q2W group who had 2 events, none of the participants had recurrent events of Oedema peripheral.

• In the dupilumab 300 mg Q2W group, none of the events were assessed by the investigator as related to the study drug.

• Potential confounders were noted for all participants in the dupilumab 300 mg Q2W group. These confounders included comorbidities (eg, chronic kidney disease, diabetes, heart failure, varicose veins) and/or treatment with medications (eg, calcium channel blockers, corticosteroids) that may increase the risk for Oedema peripheral. Considering the baseline differences in risk factors (higher incidence of chronic kidney disease and calcium channel blocker use in the dupilumab 300 mg Q2W group), along with the confounding factors associated with all events, and the resolution of all events while on the

study drug, there is insufficient evidence to establish a causal relationship between peripheral edema and dupilumab. The imbalance in similar events (Peripheral swelling and Lymphoedema) in the opposite direction supports the above findings as being stochastic in nature

Arthralgia is not considered an ADR for dupilumab in patients with BP. At the PT level, Arthralgia was reported in 5 (9.4%) participants in the dupilumab 300 mg Q2W group and 3 (5.7%) participants in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was 1.48 (0.35, 6.22).

• The baseline data revealed that Arthralgia was reported in 3 (5.7%) participants in the dupilumab 300 mg Q2W group and 0 participants in the placebo group. This suggests a potential pre-existing susceptibility to arthralgia in the dupilumab 300 mg Q2W group as compared to placebo, even before the initiation of the study treatment.

• No temporal association was observed in the occurrence of Arthralgia and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group was variable, ranging from 36 to 275 days after study drug initiation.

• None of the TEAEs resulted in discontinuation of dupilumab and 2 of the events resolved while on study drug.

• Possible confounders were identified for 4 of the 5 participants in the dupilumab 300 mg Q2W group who developed Arthralgia during the study.

– One participant with pre-existing ongoing Arthralgia reported worsening of the arthralgia on day 191. This event was mild and resolved without treatment while participant was on study drug.

– The second participant had a knee arthroplasty at baseline and additionally suffered a fall and injury of the knee on day 52. This participant experienced an event of Arthralgia in the knee on day 273 which was reported as ongoing at the data cutoff.

– The third participant with pre-existing ongoing condition of Arthralgia, that started over 50 years ago, reported worsening of Arthralgia at day 77. This event was assessed as a moderate, not related to dupilumab, and was reported as ongoing at the data cutoff.

– The fourth participant experienced an event of Arthralgia on day 275. This participant has a history of spinal laminectomy in 2022. Persistent pain occurs in as many as 40% of patients who undergo spine surgery, with higher rates of persistent pain after fusion and laminectomy compared with discectomy (Chan, 2011). The participant experienced left buttock and right knee pain concurrently. Given their previous laminectomy, the right knee pain may be referred pain caused by a spinal problem. Given the higher baseline incidence of Arthralgia in the dupilumab 300 mg Q2W group, the confounding factors associated with 4 of the events, and the resolution of most events while on study drug, there is insufficient evidence to establish a causal relationship between arthralgia and dupilumab.

Asthma is not considered an ADR for dupilumab in patients with BP. At the PT level, asthma was reported in 4 (7.5%) participants in the dupilumab 300 mg Q2W group and 1 (1.9%) participant in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was 3.37 (0.38, 30.22).

• The baseline data indicate that a higher proportion of participants in the dupilumab 300 mg Q2W group (11.3%, n=6) had pre-existing asthma compared to the placebo group (3.8%, n=2). This suggests a potential for an increased incidence of asthmarelated events in the dupilumab 300 mg Q2W group during the study.

• Two of the 4 participants in the dupilumab 300 mg Q2W group with a TEAE of Asthma had documented pre-existing asthma at baseline. A new diagnosis of asthma was observed in 1 participant three weeks following the onset of Pneumonia. Pneumonia can be a potential trigger for adult-onset asthma, and this case may represent an instance of such an association.

• No temporal association was observed in the occurrence of Asthma and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group was variable, ranging from 19 to 346 days post drug initiation.

• None of the TEAEs resulted in discontinuation of dupilumab. Of the 4 participants with a TEAE of Asthma in the dupilumab 300 mg Q2W group, 1 participant, who had preexisting asthma at baseline, reported resolution of asthma while 3 participants reported asthma as ongoing by data cutoff. In the dupilumab 300 mg Q2W group, none of the events recurred. None of these 4 events were considered by the investigator to be related to dupilumab.

Considering the higher baseline incidence of asthma in the dupilumab 300 mg Q2W group, the confounding factors associated with most of the events, and the resolution of 1 of the 4 events while on study drug, there is insufficient evidence to establish a causal relationship between asthma and dupilumab.

Back pain is not considered an ADR for dupilumab in patients with BP. At the PT level, Back pain was reported in 4 (7.5%) participants in the dupilumab 300 mg Q2W group and 2 (3.8%) participants in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was 1.64 (0.30, 8.97). At baseline there was 1 participant with Back pain in each treatment group. No temporal association was observed in the occurrence of Back pain and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group was variable, ranging from 43 to 322 days after study drug initiation. None of the TEAEs in the dupilumab 300 mg Q2W group were considered serious, severe, resulted in discontinuation of study drug, or were deemed related to study treatment. Each participant experienced only 1 event of Back pain, with 2 of these events resolved while on study drug.

Possible alternative etiologies and/or confounders were identified for 3 of 4 participants in the dupilumab 300 mg Q2W group.

• One participant with pre-existing osteoarthritis reported Back pain on day 43. This participant recovered with sequelae (degenerative lumbar spine with L4-L5 HIVD) while on study treatment. Later during the study, an additional event of spinal osteoarthritis (day 116) was reported for this participant.

• In the second participant, Back pain was reported on day 362. An event of Sciatica had been reported approximately 7 months prior to the onset of the back pain, and both the Back pain and Sciatica were ongoing at the data cutoff. The event of Back pain was assessed as unrelated to dupilumab, and the study treatment remained unchanged.

• In the third participant, the event of Back pain was reported on day 243 and occurred at the same time as a TEAE of a Fall. The participant had a pre-existing condition of muscle weakness that persisted throughout the study and may have contributed to the fall and subsequent back pain. This event was ongoing at the data cutoff.

Considering the confounding factors associated with most of the events, and the resolution of 2 of the 4 events while participants continued on dupilumab, there is insufficient evidence to establish a causal relationship between back pain and dupilumab.

Vision blurred is not considered an ADR for dupilumab in patients with BP. At the PT level, Vision blurred was reported in 4 (7.5%) participants in the dupilumab 300 mg Q2W group and 0 participants in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo was not computable, as no participants in the placebo group experienced Vision blurred.

• The baseline data indicate that the dupilumab 300 mg Q2W group had a higher prevalence of eye disorders (14 [26.4%] participants compared with 9 [17.0%] participants in the placebo group). At baseline, more participants reported Cataract in the dupilumab 300 mg Q2W group (9 [17.0%]) compared with the placebo group (6 [11.3%]). Additionally, the number of participants with cataract surgery was higher in the dupilumab 300 mg Q2W group (5 [9.4%] participants) compared with 1 (1.9%)

participant in the placebo group.

• Blurred vision is a non-specific symptom that can arise from a multitude of underlying ophthalmological conditions. Cataracts, characterized by opacification of the crystalline lens, are a common cause of progressive visual blurring. Furthermore, cataract surgery, while generally improving visual acuity, can also induce transient blurred vision as a normal postoperative sequela or due to potential complications such as posterior capsule opacification or corneal edema.

• None of the 4 reported TEAEs were considered serious, severe, or led to discontinuation of dupilumab.

• In 1 of the participants, Vision blurred occurred on study day 34. This event was moderate, nonserious, and assessed by the investigator as not related to dupilumab. The event fully resolved by day 59 while the participant was on the study drug. The second participant experienced an event of Vision blurred on day 1. The event was mild, nonserious, and assessed by the investigator as not related to dupilumab. Dosing of dupilumab was not changed and the event was resolving at the data cutoff.

• Possible confounders were identified for 2 of the 4 participants in the dupilumab 300 mg Q2W group who developed the event of Vision blurred during the study.

− One participant experienced an event of blurred vision on an unknown date. At baseline, this participant reported conditions of cataract and dry eye that were ongoing at the onset of the event of Vision blurred. This event was deemed by the investigator as not related to dupilumab, did not interrupt study treatment, and was ongoing at the data cutoff.

− The second participant developed the event of Vision blurred on study day 1. At baseline, the participant reported conditions of blurred vision and long-term myopia that were ongoing at the onset of the event of Vision blurred. It was reported that the participant had cataract operation 2 years ago and was suffering from migraines. The event was ongoing at the data cutoff.

In summary, considering the higher baseline prevalence of pre-existing eye disorders in the dupilumab 300 mg Q2W group, including cataracts and a history of cataract surgery; the confounding factors associated with 2 of the 4 events; the atypical time of onset; as well as resolution of blurred vision while continuing on dupilumab in some cases, there is insufficient evidence to establish a causal relationship between blurred vision and dupilumab. Also noteworthy, the (PT) Visual impairment (which is similar in nature to blurred vision) was reported at a numerically higher incidence in the placebo group (2/53 [3.8%]) compared with 0 in the dupilumab 300 mg Q2W group, thus supporting the stochastic nature of these observations.

Upper respiratory tract infection is not considered an ADR for dupilumab in patients with BP. At the PT level, Upper respiratory tract infection was reported in 3 (5.7%) participants in the dupilumab 300

mg Q2W group and 1 (1.9%) participant in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was 2.37 (0.25, 22.90). No temporal association was observed in the occurrence of Upper respiratory tract infection and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group ranged from 98 to 383 days post-study drug initiation. None of these TEAEs were considered serious, severe, or resulted in the discontinuation of study drug. All events resolved during the study period. One event in the dupilumab 300 mg Q2W group was considered by the investigator to be related to study drug, while 2 events were deemed not related.

• It is pertinent to note that although the incidence of Upper respiratory tract infection at the PT level was numerically higher in the dupilumab 300 mg Q2W group compared with the placebo group, the incidence was numerically lower in the dupilumab 300 mg Q2W group (8/53[15.1%]) compared with the placebo group (9/53 [17.0%]) at the level of HLT (Upper respiratory tract infection), which reflects a more comprehensive view of the concept.

• For completeness, the (HLT) Upper respiratory tract signs and symptoms were also evaluated and showed only a single PT (Dysphonia) reported in the dupilumab 300 mg Q2W group (1 [1.9%]) compared with none in the placebo group.

• Given the overlapping symptomatology, upper respiratory infections, nasopharyngitis, and COVID-19 were also assessed in aggregate. Note that the PT Nasopharyngitis is included in the HLT Upper respiratory tract infections. Review of these events collectively showed that the incidence of (HLT) Upper respiratory tract infections combined with (PT) COVID-19 was lower in the dupilumab 300 mg Q2W group (11/53 [20.8%]) compared with the placebo group (12/53 [22.6%]).

Thus, taking into consideration the following: 1) the small numerical imbalance in (PT) URTI (with the lower bound of the HR 95% CI <1); 2) the lower incidence of (HLT) URTI (both with and without combining with [PT] COVID-19) in the dupilumab 300 mg Q2W group versus the placebo group; 3) the lack of any significant findings in (HLT) Upper respiratory tract signs and symptoms; 4) all events in the dupilumab 300 mg Q2W group resolving while the participants continued on dupilumab; and 5) all events exhibiting no pattern in time to onset, there is insufficient evidence for causality with dupilumab.

Constipation is not considered an ADR for dupilumab in patients with BP. At the PT level, Constipation was reported in 4 (7.5%) participants in the dupilumab 300 mg Q2W group and 1 (1.9%) participant in the placebo group. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo was 3.80 (0.42, 34.09). No temporal association was observed in the occurrence of Constipation and dupilumab exposure. The time to onset of the events in the dupilumab 300 mg Q2W group ranged from 3 to 284 days after study drug initiation. None of these TEAEs were considered serious, severe, or led to the discontinuation of study drug. At the time of reporting, in the dupilumab 300 mg Q2W group, 2 events were ongoing, while the remaining 2 had resolved during the study period. None of these TEAEs were considered related to study drug by the investigator. Possible alternative etiologies and/or confounders were identified in 2 of 4 participants: 2 participants had received concomitant NSAIDs which are associated with constipation (Fosnes, 2011). Constipation is a common problem in the elderly population and the mean age of the enrolled participants in this study was 71 years. The small numerical difference between groups most likely reflects either a stochastic difference or, possible baseline differences in the myriad of factors that contribute to this common problem. The following events did not meet either of the quantitative criteria but were selected for further review based on clinical relevance.

Keratitis is not considered an ADR for dupilumab in patients with BP. A CMQ was used to search for similar medical concepts, however, Keratitis was the only PT which was identified by the keratitis cluster. Keratitis (PT) was reported in 2 (3.8%) participants in the dupilumab 300 mg Q2W group and

0 participants in the placebo group. At the PT level, the hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo was not computable, as no participants in the placebo group experienced Keratitis. All events had important confounders, 1 was considered by the investigator to be related to dupilumab, and no events led to study drug discontinuation. In summary, considering the small numerical imbalance and confounding factors in both cases, there is insufficient evidence to establish a causal relationship between keratitis and dupilumab.

Herpes Viral infections: Herpes simplex typically demonstrates frequent reactivation with disease manifestations similar to the initial infection, often localized to the original site. Its incidence declines with age, and reactivation is triggered by various environmental and physiological factors. In contrast, Herpes zoster typically reactivates later in life, often only once, and its incidence increases with age and declining cellular immunity. Reactivation of Herpes zoster results in a clinically distinct disease that can occur anywhere on the body, with broader ganglionic spread and larger lesions. Certain comorbidities, such as diabetes, have been shown to increase the risk for herpes zoster (Papagianni, 2018) (Saadatian-Elahi, 2020). This divergent behavior underscores the need for independent assessment of these viruses in research and clinical practice. The baseline data indicate that the dupilumab 300 mg Q2W group had a higher proportion of participants taking immunosuppressants (13 [24.5%] participants in the dupilumab 300 mg Q2W group vs 6 [11.3%] participants in the placebo group) and selective immunosuppressants (4 [7.5%] participants in the dupilumab 300 mg Q2W group vs none in the placebo group). This suggests a potential pre-existing susceptibility to herpes viral infections in the dupilumab 300 mg Q2W group even before the initiation of the study treatment.

• **Herpes zoster** is not considered an ADR for dupilumab in patients with BP. At the PT level, Herpes zoster was observed in 2 (3.8%) participants receiving dupilumab and 0 participants receiving placebo. The hazard ratio (95% CI) of dupilumab 300 mg Q2W versus placebo group was not computable, as no participants in the placebo group experienced Herpes zoster. Neither of these TEAEs were considered serious, related to study drug, or led to the discontinuation of study drug.

− The first participant with Herpes Zoster was a 75-year-old female who reported experiencing an event of Steroid diabetes (PT) on study day 22. Dupilumab dose was not changed and this event subsequently resolved with treatment on study day 84. On study day 303, mild Herpes zoster was reported and treatment included bacitracin, valaciclovir, and sulfadiazine silver. Dosing with dupilumab was not

changed and the event of Herpes Zoster subsequently resolved on study day 350. The participant was treated with dupilumab and OCS throughout the event, with the most recent dose of dupilumab received on study day 351. Given the participant's risk factors, including age and OCS use, along with resolution of the event while on active treatment, the event of Herpes zoster is unlikely to be related to dupilumab.

− The second participant was an 84-year-old male with a medical history of diabetes who reported a right knee septic arthritis on study day 55 that was ongoing. On study day 230, an event of Herpes zoster of moderate intensity was reported. This was treated with famciclovir and the event subsequently resolved on study day 240. The participant continued on study drug without any interruption with no subsequent reoccurrence of Herpes zoster.

− The risk factors for Herpes zoster, including advancing age, diabetes, and use of OCS, are relevant to both the placebo and dupilumab 300 mg Q2W groups. Given the small number of events, and both events resolved while on dupilumab, and continued dosing with dupilumab did not elicit a reoccurrence, evidence is insufficient to establish a relationship between herpes zoster and dupilumab, and this observation is likely stochastic in nature.

• **Herpes simplex** is not considered an ADR for dupilumab in patients with BP. Two herpes simplex viral infections were reported, one event of Herpes simplex in 1 participant and Oral herpes in another participant. Both cases were in the dupilumab 300 mg Q2W group and were treated with acyclovir.

− In 1 participant, onset of Herpes simplex occurred on study day 57. The event, considered by the investigator as mild, nonserious, and unrelated to dupilumab, resolved on study day 70. From baseline to day 52, the participant received colchicine, a drug which has been associated with myelosuppression,

granulocytopenia, and leukopenia, as indicated in the product label. The participant was also receiving ongoing treatment with OCS. No change to dupilumab administration was made and the participant continued treatment with the last dose on study day 295 with no further reoccurrence.

− In another participant, onset of Oral herpes occurred on study day 159. The event, considered by the investigator as mild, nonserious, and related to dupilumab, resolved on study day 165. Treatment with dupilumab was not changed due to this event. The participant continued treatment with the last dose on study day 309 with no further reoccurrence of the event.

− Given the small number of events; the higher use of immunosuppressants at baseline in the dupilumab 300 mg Q2W group; both events reported as resolved while on study drug; continued dosing not eliciting a reoccurrence; and a confounding factor in 1 of the cases, there is insufficient evidence to establish a relationship between herpes simplex and dupilumab, and this observation is likely stochastic in nature.

The safety profile of dupilumab is well characterized across multiple indications and the data support dupilumab as not having an immunosuppressive effect. Overall, the data from the R668-BP-1902 study support this observation. The incidence of infections at the SOC level is similar between the 2 treatment groups. The underlying HLT level data do not reveal any clear pattern; some AEs by HLTs were observed in a higher proportion of participants in the dupilumab 300 mg Q2W group, others in the placebo group, and some were similar between the treatment groups. These observations support the numerical differences in herpes-related events in the R668-BP-1902 study as being stochastic in nature, rather than causally linked to dupilumab.

Other events previously established as ADRs for approved indications were either not reported in the dupilumab 300 mg Q2W group of Study R668-BP-1902 (conjunctivitis allergic, conjunctivitis bacterial, blepharitis, eye pruritus, serum sickness reactions, serum sickness-like reactions, angioedema, ulcerative keratitis, facial rash), or were reported with similar incidences between the dupilumab 300 mg Q2W and placebo groups, including injection site reactions, that included reactions of bruising, erythema, and swelling all seen in 1 participant (dupilumab 300 mg Q2W: 1 [1.9%] participant; placebo: 1 [1.9%] participant), Dry eye (dupilumab: 1 [1.9%] participant; placebo: 2 [3.8%] participants), and Eosinophilia (dupilumab: 1 [1.9%] participant; placebo: 1 [1.9%] participant).

In summary, based on consideration of previously established ADRs in other indications and analysis of safety data from Study R668-BP-1902, conjunctivitis (dupilumab 300 mg Q2W group: 4 [7.5%]; placebo; 0) was identified as an ADR for dupilumab in participants with BP.

Laboratory findings

Hematology

Mean/Median Changes from Baseline

In Study R668-BP-1902, there were no consistent or clinically meaningful trends within or differences between treatment groups for any of the hematology parameters during the on-treatment period through week 52 up to data cutoff:

• RBC parameters (MCHC, MCH, MCV, RBC count, hematocrit, hemoglobin, and platelets)

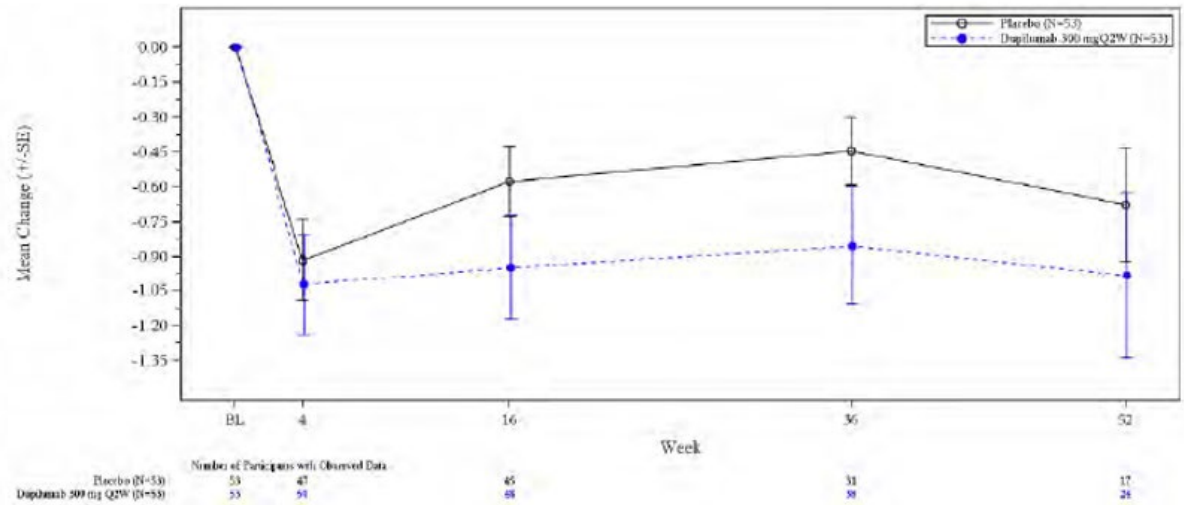
• WBC parameters (basophil, eosinophil [for further details, see below], leukocyte, lymphocyte, monocyte, and neutrophil counts).

In some dupilumab studies/indications, transient initial increases from baseline in the mean blood eosinophil counts followed by a return to baseline during the treatment period have been observed in dupilumab-treated participants. Of note, the eosinophil results in R668-BP-1902 need to be interpreted in the context of OCS use in this study, where all participants in both treatment groups received OCS starting from baseline with the objective to taper off by week 16 as per the protocol.

Systemic corticosteroids are known to decrease blood eosinophil counts (Schleimer, 1994).

Mean (SD) eosinophil count at baseline was 0.9430×109/L (1.16090) and 1.1046×109/L (1.48220) in the placebo and dupilumab 300 mg Q2W groups, respectively. The mean values in both treatment groups were above the ULN of 0.8 ×109/L, which is consistent with reports of elevated type 2 inflammatory markers in published literature on patients with BP (Kridin, 2018). As expected with initiation of OCS, a rapid decrease from baseline in the mean eosinophil count was observed at week 4 in both treatment groups (placebo: -0.9147×109/L; dupilumab 300 mg Q2W: -1.0221×109/L). The eosinophil counts did not return to baseline during the on-treatment period through week 52 up to the data cutoff, with larger mean decreases observed in the dupilumab 300 mg Q2W group versus the placebo group (eg, mean change from baseline to week 52 values for placebo: -0.6768×109/L and for dupilumab 300 mg Q2W: -0.9813×109/L) (Figure 19).

Figure 19. Line Chart: Mean (SE) Change in Eosinophils (109/L) During the On-Treatment Period Through Week 52 up to Data Cutoff in Study R668-BP-1902 (SAF)



Abbreviations: BL=baseline; Q2W=every 2 weeks; SAF=safety analysis set; SE=standard error.

Shifts from Baseline

There were no clinically meaningful trends in shifts from baseline within or between treatment groups during the on-treatment period through week 52 up to data cutoff in RBC or WBC parameters.

Potentially Clinically Significant Values

RBC Parameters and Platelets

For RBC parameters and platelets, the proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff was similar in both treatment groups: 11/51 participants (21.6%) in the placebo group and 8/53 participants (15.1%) in the dupilumab 300 mg Q2W group. The most frequently identified PCSVs for RBC parameters and platelets in both groups were related to PCSV decreases from baseline in hemoglobin (5 participants in the placebo group and 4 participants in the dupilumab 300 mg Q2W group had a ≥20 g/L decrease from baseline and 3 participants in each group had a decrease defined as >115 g/L/>95 g/L at baseline decreasing to ≤115 g/L/≤95 g/L in males/females, respectively), hematocrit (5 participants in the placebo group and 3 participants in the dupilumab 300 mg Q2W group), and erythrocytes (4 and 3 participants, respectively). 3 participants had treatment-emergent PCSVs for hematology parameters that were reported as TEAEs of Anaemia:

• 1 participant in the placebo group had a moderate TEAE of Anaemia assessed by the investigator as not related to study drug

• 2 participants in the dupilumab 300 mg Q2W group had treatment-emergent PCSVs

for hematology parameters that were reported as TEAEs of Anaemia: 1 had 2 TEAEsof Anaemia of mild intensity, 1 was assessed by the investigator as related and the other as not related to study drug and another participant had a mild TEAE of Anaemia assessed by the investigator as not related to study drug.

WBC Parameters

For WBC parameters, the proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff was similar for both treatment groups: 16/51 participants (31.4%) in the placebo group and 21/53 participants (39.6%) in the dupilumab 300 mg Q2W group. The most frequently identified PCSVs in both groups were related to PCSV increases from baseline in monocytes (5 participants in the placebo group and 13 participants in the dupilumab 300 mg Q2W group), basophils (5 participants and 9 participants, respectively), lymphocytes (5 and 3 participants, respectively), and leukocytes (4 and 3 participants, respectively).

3 participants (2 participants in the placebo group and 1 participant in the dupilumab 300 mg Q2W group) had PCSV increases in eosinophils. For all 3 participants, these increases were transient, with eosinophil counts returning to normal ranges by the participant's final visit, and were not associated with clinical symptoms and did not require study drug interruption or discontinuation. 1 participant in the placebo group had a PCSV for leukocytes that was reported as a mild TEAE of Leukocytosis and 1 participant in the dupilumab 300 mg Q2W group had a PCSV for leukocytes that was reported as a moderate TEAE of Leukocytosis. Both events were assessed by the investigator as not related to study drug.

2 participants in the placebo group and 3 participants in the dupilumab 300 mg Q2W group had a post baseline peak blood eosinophil count ≥1000 per microliter (1.0×109/L) during the study, one of whom (in the placebo group) had a peak blood eosinophil count ≥5000 per microliter (5.0×109/L) (Table 50). Of note, mean (SD) baseline blood eosinophil counts were increased, with values of 0.9430×109/L (1.16090) in the placebo group and 1.1046×109/L (1.48220) in the dupilumab 300 mg Q2W group.

None of these elevations were clinically symptomatic, did not require study drug interruption or discontinuation, were not reported as AEs, and did not meet the criteria for an AESI.

Table 50. Number of Participants with Blood Eosinophil Counts ≥1000 or ≥5000 cells per Microliter During the On-Treatment Period Through Week 52 up to Data Cutoff in Study R668-BP-1902 (SAF)

Number of Participants	Placebo (N=53)	Dupilumab 300 mg Q2W (N=53)
Eosinophils ≥1000 per microliter	2 (3.8%)	3 (5.7%)
Eosinophils ≥5000 per microliter	1 (1.9%)	0

Note: Baseline visit values are excluded. The values in SI units are: 1000 cells/μL=1.0×10^9/L and 5000 cells/μL=5.0×10^9/L.
Abbreviations: Q2W=every 2 weeks; SAF=safety analysis set

Chemistry

Mean/Median Changes from Baseline

In Study R668-BP-1902, there were no consistent or clinically meaningful trends in either treatment group for any of the clinical chemistry parameters during the on-treatment period through week 52 up to data cutoff:

• Liver function (ALT, alkaline phosphatase, AST, bilirubin, and LDH)

• Renal function (creatinine, urate, and urea nitrogen)

• Electrolytes (bicarbonate, calcium, chloride, potassium, and sodium)

• Metabolic function (albumin, C-reactive protein, creatine kinase, glucose, hemoglobin A1C, and protein)

• Lipids (cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides)

Shifts from Baseline

There were no clinically meaningful trends in shifts from baseline within or between treatment groups during the on-treatment period through week 52 up to data cutoff for any of the clinical chemistry parameters (Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR Section 5.2.3.2.2).

Potentially Clinically Significant Values Liver Function

There was a low proportion of participants with PCSV liver function values in both treatment groups: 1/51 participant (2.0%) in the placebo group and 4/53 participants (7.5%) in the dupilumab 300 mg Q2W group had at least 1 PCSV for liver function

• In the placebo group, 1 participant had a PCSV of increased bilirubin at week 4. Other liver enzyme values were within the normal range at this visit.

• In the dupilumab 300 mg Q2W group, 4 participants had PCSVs identified, as follows:

– 2 participants had PCSVs for increased alkaline phosphatase alone (>1.5 ULN and ≤1.5 ULN at baseline), 1 participant at week 36 and 1 at week 52; subsequent values remained above the ULN but were not PCSVs. The first participant had a PCSV of 174 IU/L at week 36. This participant had alkaline phosphatase values >ULN (ie, >115 IU/L) at all assessments from screening through week 52 (with values between 130 IU/L and 168 IU/L). All ALT, AST, and bilirubin values were within the normal range. The second participant had a PCSV of 174 IU/L at week 52. This participant had alkaline

phosphatase values >ULN at all other assessments from baseline through week 64 (with values between 121 IU/L and

160 IU/L), except for week 16 (value of 110 IU/L). All ALT, AST, and bilirubin values were within the normal range, except for an increased ALT value at day 1 of 46 IU/L (ULN was 40 IU/L). Neither participant had any associated hepatic TEAEs and study drug was not interrupted or discontinued due to the PCSVs.

− 1 participant had single treatment-emergent PCSVs for ALT (PCSV value of 237 IU/L [between >5 ULN and ≤10 ULN and ≤5 ULN at baseline; ULN was 33 IU/L]) and AST (PCSV value of 167 IU/L [between >3 ULN and ≤5 ULN and ≤3 ULN at baseline; ULN was 36 IU/L]) at an unscheduled visit on study day 3.

By week 4, both parameters were within the normal range with further minor elevations at week 36 (ALT only) and week 52 (ALT and AST) which normalized again at week 64 (end of study). Alkaline phosphatase values were above ULN at all visits from baseline to week 64 except for week 16. Bilirubin values were within the normal range at all visits. The PCSVs were reported as a severe TEAE (Drug-induced liver injury) on study day 3 that resolved on study day 12. Study drug was not interrupted or discontinued due to the PCSVs.

− 1 participant had multiple treatment-emergent PCSVs for alkaline phosphatase (at weeks 4, 16, at 2 unscheduled visits on days 196 and 224, and at week 36) with values of between 186 IU/L at week 36 and 730 IU/L on study day 196. Elevated alkaline phosphatase values were also reported at screening, day -1 and day 280 that were not PCSVs. On study day 196, the participant also had treatmentemergent

PCSVs for ALT (PCSV of 309 IU/L) and AST (PCSV of 164 IU/L); both parameters had returned to within the normal range by week 36. Elevated ALT values were also reported at day -1 and day 224 and elevated AST values at screening, day -1, and day 224 which were not PCSVs. Bilirubin levels were

within the normal range at all visits. The PCSV for increased alkaline phosphatase at week 16 (day 112) of 329 IU/L was reported as a mild TEAE of Blood alkaline phosphatase increased that was ongoing at data cutoff. The participant had mild pre-baseline AEs of Aspartate aminotransferase increased and Alanine aminotransferase increased that both resolved by day 14. A TEAE of moderate Chronic hepatitis was reported on study day 178 that was ongoing at data cutoff and led to interruption of study drug from study day 182 to 288. All the above listed events were assessed by the investigator as unrelated to study drug.

Renal Function

For renal function parameters, the proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff was similar for both treatment groups: 13/51 participants (25.5%) in the placebo group and 17/53 participants (32.1%) in the dupilumab 300 mg Q2W. The most frequently identified PCSVs in both groups were related to PCSV increases from baseline in:

• Serum creatinine (≥30%, but <100%, increase from baseline): 7 participants in the placebo group and 11 participants in the dupilumab 300 mg Q2W group. Of these, only 2 participants (both in the dupilumab 300 mg Q2W group) had increases which exceeded the ULN: 1 participant with a day 1 serum creatinine level of 115 µmol/L (normal range 62 to 124 µmol/L) had an increase to 133 µmol/L at week 16, followed by a decrease to within normal ranges (value: 106 µmol/L) at week 36. 1 participant with a day 1 serum creatinine level of 88 µmol/L had an increase to 141 µmol/L at week 52; the participant did not have any further visits after this time point.

• Urate (>408 µmol/L and ≤408 µmol/L at baseline): 5 participants in the placebo group and 7 participants in the dupilumab 300 mg Q2W group 1 participant in the placebo group had treatment-emergent PCSVs for renal parameters (creatinine and urea nitrogen) and a concurrent moderate AE (reported after the end-of-study visit) of Blood urea increased. The event was assessed by the investigator as not related to study drug.

Electrolytes

The proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff for electrolyte parameters was similar for both treatment groups: 4/51 participants (7.8%) in the placebo group and 3/53 participants (5.7%) in the dupilumab 300 mg Q2W group. The most frequently identified PCSV in the placebo group was decreased sodium (in 4 participants). The only PCSV reported in the dupilumab 300 mg Q2W group was increased potassium (in 3 participants). No participants had a treatment-emergent PCSV relating to electrolytes that was reported as a TEAE.

Metabolic Function

The proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff for metabolic parameters was similar for both treatment groups: 15/51 participants (29.4%) in the placebo group and 11/53 participants (20.8%) in the dupilumab 300 mg Q2W group. The most frequently identified PCSVs in both groups were related to PCSV increases from baseline in C-reactive protein (9 participants in the placebo group and 6 participants in the dupilumab 300 mg Q2W group) and increases in hemoglobin A1C (5 participants in the placebo group and 4 participants in the dupilumab 300 mg Q2W group).

Lipids

The proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff for lipid parameters was similar in both treatment groups:

4/51 participants (7.8%) in the placebo group and 8/53 participants (15.1%) in the dupilumab 300 mg Q2W group.

The most frequently identified PCSV in both groups was increased cholesterol (3 participants in the placebo group and 8 participants in the dupilumab 300 mg Q2W group). 1 participant in the placebo group had a treatment-emergent PCSV for triglycerides that was reported as a moderate AE (reported after the end-of-study visit) of Blood triglycerides increased. The event was assessed by the investigator as not related to study drug.

Urinalysis

There were no clinically meaningful trends within or between treatment groups in mean/median changes from baseline in urine specific gravity or pH during the on-treatment period through week 52 up to data cutoff. There were also no clinically meaningful trends in shifts from baseline in urine specific gravity between treatment groups and no participants with treatment-emergent PCSVs in urinalysis parameters.

Vital signs and physical findings

Vital Signs

Mean/Median Changes from Baseline

There were no clinically meaningful trends within or between treatment groups in mean/median changes from baseline in vital signs during the on-treatment period through week 52 up to data cutoff.

Potentially Clinically Significant Values

The proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff for vital signs was comparable in both treatment groups: 37/52 participants (71.2%) in the placebo group and 36/53 participants (67.9%) in the dupilumab 300 mg Q2W group). The most frequently identified PCSVs for vital signs in both groups were related to PCSV increases in systolic blood pressure (14 participants in the placebo group and 19 participants in the dupilumab 300 mg Q2W group) and increases in weight (10 participants in the placebo group and 13 participants in the dupilumab 300 mg Q2W group).

• 4 participants in the placebo group had a treatment-emergent PCSV in the category of systolic or diastolic blood pressure which was also reported as a TEAE (3 TEAEs of Hypertension and 1 of White coat hypertension). 3/4 of these participants had a medical history of hypertension.1 participant in the placebo group had a treatment emergent PCSV in the category of weight which was reported as a TEAE of Weight

decreased. All events were assessed by the investigator as not related to study drug.

• 2 participants in the dupilumab 300 mg Q2W group had treatment-emergent PCSVs in the categories of systolic and diastolic blood pressure that were reported as TEAEs (Hypertension in 1 participant and events of Blood pressure increased, Hypertensive crisis, Blood pressure fluctuation, and Hypotension in 1 participant) which were assessed by the investigator as not related to study drug.

Electrocardiogram

Mean/Median Changes from Baseline

There were no clinically meaningful trends or differences between treatment groups in mean/median changes from baseline in ECG parameters during the on-treatment period through week 52 up to data cutoff.

Shifts from Baseline

There were no clinically meaningful trends in shifts from baseline in ECG parameters between treatment groups during the on-treatment period through week 52 up to data cutoff. 15/53 participants in the placebo group and 24/53 participants in the dupilumab 300 mg Q2W group had an abnormal ECG reading at baseline.

Potentially Clinically Significant Values

The proportion of participants with at least 1 treatment-emergent PCSV during the on-treatment period through week 52 up to data cutoff for ECGs was slightly higher in the dupilumab 300 mg Q2W group (20/48 participants [41.7%]) versus the placebo group (15/48 participants [31.3%]). The most frequently identified PCSVs for ECG parameters in both treatment groups were related to PCSV prolongation of the QTcB interval, as follows:

• Borderline PCSV prolongation (431-450 ms and <431 ms at baseline for male participants; 451-470 ms and <451 ms at baseline for female participants): 3 participants in the placebo group and 5 participants in the dupilumab 300 mg Q2W group

• Prolonged PCSVs (>450-<500 ms and ≤450 ms at baseline for male participants; >470-<500 ms and ≤470 ms at baseline for female participants): 4 participants in the placebo group and 2 participants in the dupilumab 300 mg Q2W group

• PCSVs for borderline increases of between 30 ms and 60 ms: 4 participants in the placebo group and 7 participants in the dupilumab 300 mg Q2W group

1 participant in the dupilumab 300 mg Q2W group had a treatment-emergent PCSV for a borderline increase from baseline of 30-60 ms for the QTcB interval on the same day as a mild TEAE of Myocardial infarction (VT: abnormal ECG suggestive of possible septal infarct). The event was assessed by the investigator as not related to study drug.

Physical Examination

Physical Examination Shifts from Baseline

No clinically meaningful shifts in physical examination findings from baseline during the on-treatment period through week 52 up to data cutoff were observed in either treatment group.

Immunogenicity

Immunogenicity and Safety

The overall incidence of treatment-emergent ADA in participants treated with dupilumab 300 mg Q2W in Study R668-BP-1902 was 3.8% (2/52 participants), with both participants classified as having an indeterminate response. 1 participant had a low maximum titer level while the other had a moderate maximum titer level; both were NAb positive.

As treatment-emergent ADA-positive responses were noted in only 2 participants in the dupilumab 300 mg Q2W group (<5%), potential associations between immunogenicity and safety 3) were not performed, as defined in the Statistical Analysis Plan.

The AE profiles of participants with ADA-positive responses were examined at the individual participant level. Of the 2 participants in the dupilumab 300 mg Q2W group who were ADA positive, neither had TEAEs potentially associated with positive ADA status during the study.

Safety in special populations

Subgroup Analyses

Frequency of Treatment-Emergent Adverse Events by Age

Overall, in Study R668-BP-1902, dupilumab 300 mg Q2W was well tolerated in elderly (≥65 years) participants (Table 51 below). There was a low number of participants aged <65 years in this study, with 77.4% (82/106) of participants aged ≥65 years. There were no notable differences in the frequency of TEAEs reported between age groups, or between treatment groups by age.

Table 51. Summary of Treatment-Emergent Adverse Events Reported by ≥5% of Participants in any Treatment Group by Age Group and Overall: by Primary SOC and PT During the On-Treatment Period Through Week 52 up to Data Cutoff in Study R668-BP-1902 (SAF)

Primary System Organ Class Preferred Term	Placebo (n=53)	Dupilumab 300 mg Q2W (n=53)	Placebo (n=11)	Dupilumab 300 mg Q2W (n=13)	Placebo (n=42)	Dupilumab 300 mg Q2W (n=40)
AGE GROUP	Overall		<65 years		≥65 years	
Number of participants with at least 1 TEAE	51 (96.2%)	51 (96.2%)	10 (90.9%)	13 (100%)	41 (97.6%)	38 (95.0%)
Infections and infestations	27 (50.9%)	28 (52.8%)	7 (63.6%)	8 (61.5%)	20 (47.6%)	20 (50.0%)
Nasopharyngitis	8 (15.1%)	7 (13.2%)	3 (27.3%)	3 (23.1%)	5 (11.9%)	4 (10.0%)
Conjunctivitis	0	4 (7.5%)	0	1 (7.7%)	0	3 (7.5%)
COVID-19	3 (5.7%)	3 (5.7%)	1 (9.1%)	2 (15.4%)	2 (4.8%)	1 (2.5%)
Upper respiratory tract infection	1 (1.9%)	3 (5.7%)	0	1 (7.7%)	1 (2.4%)	2 (5.0%)
Oral candidiasis	3 (5.7%)	2 (3.8%)	2 (18.2%)	0	1 (2.4%)	2 (5.0%)
Cellulitis	3 (5.7%)	0	0	0	3 (7.1%)	0
Gastroenteritis	3 (5.7%)	0	2 (18.2%)	0	1 (2.4%)	0
Skin and subcutaneous tissue disorders	26 (49.1%)	25 (47.2%)	7 (63.6%)	4 (30.8%)	19 (45.2%)	21 (52.5%)
Pemphigoid	12 (22.6%)	6 (11.3%)	3 (27.3%)	1 (7.7%)	9 (21.4%)	5 (12.5%)
Pruritus	4 (7.5%)	3 (5.7%)	1 (9.1%)	0	3 (7.1%)	3 (7.5%)
Intertrigo	3 (5.7%)	0	2 (18.2%)	0	1 (2.4%)	0
Gastrointestinal disorders	17 (32.1%)	18 (34.0%)	5 (45.5%)	3 (23.1%)	12 (28.6%)	15 (37.5%)
Diarrhea	6 (11.3%)	6 (11.3%)	0	1 (7.7%)	6 (14.3%)	5 (12.5%)
Constipation	1 (1.9%)	4 (7.5%)	0	0	1 (2.4%)	4 (10.0%)
Abdominal pain upper	3 (5.7%)	2 (3.8%)	1 (9.1%)	0	2 (4.8%)	2 (5.0%)
Nausea	3 (5.7%)	1 (1.9%)	1 (9.1%)	0	2 (4.8%)	1 (2.5%)
Musculoskeletal and connective tissue disorders	11 (20.8%)	17 (32.1%)	3 (27.3%)	4 (30.8%)	8 (19.0%)	13 (32.5%)
Arthralgia	3 (5.7%)	5 (9.4%)	1 (9.1%)	2 (15.4%)	2 (4.8%)	3 (7.5%)
Back pain	2 (3.8%)	4 (7.5%)	0	1 (7.7%)	2 (4.8%)	3 (7.5%)
Injury, poisoning and procedural complications	15 (28.3%)	16 (30.2%)	2 (18.2%)	2 (15.4%)	13 (31.0%)	14 (35.0%)
Fall	8 (15.1%)	6 (11.3%)	1 (9.1%)	1 (7.7%)	7 (16.7%)	5 (12.5%)
Limb injury	2 (3.8%)	3 (5.7%)	0	1 (7.7%)	2 (4.8%)	2 (5.0%)

Primary System Organ Class Preferred Term	Placebo (n=53)	Dupilumab 300 mg Q2W (n=53)	Placebo (n=11)	Dupilumab 300 mg Q2W (n=13)	Placebo (n=42)	Dupilumab 300 mg Q2W (n=40)
AGE GROUP	Overall		<65 years		≥65 years	
General disorders and administration site conditions	13 (24.5%)	13 (24.5%)	2 (18.2%)	3 (23.1%)	11 (26.2%)	10 (25.0%)
Oedema peripheral	5 (9.4%)	8 (15.1%)	0	2 (15.4%)	5 (11.9%)	6 (15.0%)
Nervous system disorders	14 (26.4%)	13 (24.5%)	2 (18.2%)	2 (15.4%)	12 (28.6%)	11 (27.5%)
Headache	5 (9.4%)	4 (7.5%)	0	0	5 (11.9%)	4 (10.0%)
Metabolism and nutrition disorders	13 (24.5%)	12 (22.6%)	2 (18.2%)	1 (7.7%)	11 (26.2%)	11 (27.5%)
Hyperglycaemia	4 (7.5%)	1 (1.9%)	0	0	4 (9.5%)	1 (2.5%)
Decreased appetite	4 (7.5%)	0	0	0	4 (9.5%)	0
Eye disorders	8 (15.1%)	10 (18.9%)	0	1 (7.7%)	8 (19.0%)	9 (22.5%)
Vision blurred	0	4 (7.5%)	0	0	0	4 (10.0%)
Cataract	4 (7.5%)	1 (1.9%)	0	0	4 (9.5%)	1 (2.5%)
Vascular disorders	9 (17.0%)	10 (18.9%)	2 (18.2%)	2 (15.4%)	7 (16.7%)	8 (20.0%)
Hypertension	3 (5.7%)	4 (7.5%)	0	1 (7.7%)	3 (7.1%)	3 (7.5%)
Respiratory, thoracic and mediastinal disorders	9 (17.0%)	9 (17.0%)	4 (36.4%)	4 (30.8%)	5 (11.9%)	5 (12.5%)
Asthma	1 (1.9%)	4 (7.5%)	1 (9.1%)	1 (7.7%)	0	3 (7.5%)
Dyspnoea	3 (5.7%)	0	0	0	3 (7.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (11.3%)	6 (11.3%)	1 (9.1%)	2 (15.4%)	5 (11.9%)	4 (10.0%)
Basal cell carcinoma	3 (5.7%)	1 (1.9%)	0	0	3 (7.1%)	1 (2.5%)
Psychiatric disorders	6 (11.3%)	6 (11.3%)	3 (27.3%)	2 (15.4%)	3 (7.1%)	4 (10.0%)
Insomnia	2 (3.8%)	3 (5.7%)	1 (9.1%)	1 (7.7%)	1 (2.4%)	2 (5.0%)

MedDRA (Version 27.0) coding dictionary applied.
At each level of participant summarization, a participant is counted once if the participant reported one or more events.
Sorted by decreasing frequency at all levels in the overall dupilumab 300 mg Q2W group.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; SAF=safety analysis set; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-BP-1902 Primary Analysis CSR PTTs 14.3.2.1.b and 14.3.2.1.1.b

Additional Subgroup Analyses in Study R668-BP-1902

There were no clinically meaningful differences in the frequency of TEAEs reported within or between the subgroups of sex, ethnicity, race, baseline weight group or region.

Safety related to drug-drug interactions and other interactions

No new data are applicable to this submission.

Discontinuation due to adverse events

The proportion of participants who had at least 1 TEAE leading to permanent study drug discontinuation during the on-treatment period through week 52 up to data cutoff was higher in the placebo group versus the dupilumab 300 mg Q2W group (11.3% [6/53] vs 5.7% [3/53]). In the placebo group, 2 participants had TEAEs of Pemphigoid, and 1 participant each had General physical

health deterioration, COVID-19, Oropharyngeal cancer, and Prostate cancer leading to permanent study drug discontinuation. In the dupilumab 300 mg Q2W group, 1 participant each had TEAEs of Acute generalised exanthematous pustulosis, Angina pectoris, cardiac arrest leading to permanent study drug discontinuation. . The participant with a severe TE-SAE of Cardiac arrest leading to study drug discontinuation was reclassified from not treatment-emergent to occurring during the on-treatment period based on additional information received after the primary analysis cutoff date. For 2 participants (placebo: n=1; dupilumab 300 mg Q2W: n=1), TEAEs leading to study drug discontinuation were not reported in the on-treatment period:

• For the participant in the placebo group, the event of Meningitis cryptococcal was reported during the follow-up period, as the last dose of study drug before the event was >14 days prior.

• For the participant in the dupilumab 300 mg Q2W group, the event of Cardiac arrest was incorrectly recorded as after the end-of-study date, despite occurring on treatment. On study day 30, a non-serious AE of Gastric ulcer was reported and the participant was admitted to the hospital due to worsening anemia and subsequently underwent colonoscopy with gastrointestinal tract endoscopy. Post-procedure, during the period of medical observation, the participant experienced a severe SAE of Cardiac arrest. Cardiac massage was performed as a corrective procedure and the event was reported as resolved on the same day. The investigator considered the SAE of Cardiac arrest not related to the study drug. The only TEAE leading to study drug discontinuation considered related to study drug by the investigator was an event of Acute generalised exanthematous pustulosis in a participant in the dupilumab 300 mg Q2W group. Similar findings were observed upon review of the exposure-adjusted incidence rates of TEAEs leading to study drug discontinuation.

Post marketing experience

Dupilumab was first approved by the US FDA on 28 Mar 2017 for the treatment of adults with moderate-to-severe AD and has received subsequent approvals in other indications (asthma, CRSwNP, PN, EoE, COPD and CSU) in multiple countries/regions. Dupilumab is currently not approved for the treatment of BP in participants aged 18 years and older in any country. No new safety concerns have been identified from the post-marketing data in the most recently submitted Global PBRER for dupilumab which covered the period from 29 Mar 2024 to 28 Mar 2025. The benefit-risk profile of dupilumab across all authorized indications as of 28 Mar 2025 remains favourable.

6.1. Discussion on clinical safety

The safety data of the current submission emerge from a single pivotal trial R668-BP-1902 conducted in participants with moderate-to-severe bullous pemphigoid (BP). The study was designed as follows: A 35-day screening period is followed by a 52-week double-blind treatment period, and a 12-week post-treatment follow-up period. The primary endpoint of this study was the proportion of participants achieving sustained remission at week 36, while off OCS. The safety results represent all available safety data during the on-treatment period through week 52 up to the data cut-off on 12 July 2024 and 05 January 2025, respectively. At the time of this data cut-off, all 106 study participants had completed the study visits through week 36 of the treatment period or had alternatively discontinued early from study participation.

BP is overall a rare disease, however, the most common autoimmune subepidermal blistering disease of the skin and mucous membranes. It has an estimated prevalence of 1/4.000 in Europe. The incidence in Europe is ca. 10-34/1 million and strongly depends on the age, as it increases by age and currently ranges between 2-22/1 million or more worldwide. The applicant included a total of 106

participants in the study, randomized 1:1 to dupilumab 300 mg Q2W or placebo. The total participant number appears relatively low as measured by the prevalence.

More participants assigned to the dupilumab group completed the study treatment period through week 36 and 52, compared to the placebo group. Thus, slightly more participants in the dupilumab group received study treatment through week 36 as compared to the placebo group. Premature study drug discontinuation was more frequently reported in the placebo group; reasons for study drug discontinuation in both treatment groups were rarely reported due to adverse events.

The primary safety analysis as discussed in the following is based on, a total of 65 (61.3%) participants had completed the study through week 52. During the procedure, the applicant submitted further safety data with data cut-off 05 January 2025, i.e. global end of study, with 82/106 patients completing study through week 52 which were consistent with the primary analysis .

The exposure in both treatment groups is rather acceptable as regards the comparability of the safety results in this indication. The total exposure is, however limited. Thus, results need to be interpreted in the context of the hitherto known safety profile of dupilumab.

The demographic and baseline disease characteristics were fairly balanced between both treatment groups. Baseline disease characteristics were balanced between the treatment groups and reflect a considerable disease burden.

In both treatment groups, similar proportions of study participants experienced ≥1 treatment-emergent adverse events (TEAEs) during the on-treatment period through week 52. The majority of these were mild-to-moderate in severity. Treatment-emergent serious adverse events (TESAEs) occurred more frequently in the placebo group as well as TEAE leading to study drug discontinuation. One death was reported in the placebo group throughout the treatment phase, none in the dupilumab group but two in the follow-up period (see below). Only treatment-related TEAEs occurred more frequently in the dupilumab group, however, no treatment-related TESAEs were observed. Exposure-adjusted incidence rates show similar results.

Preferred terms (PT) with a higher incidence in the dupilumab group were Conjunctivitis (7.5% vs. 0%), a known ADR, Vision blurred (7.5% vs. 0%), Keratitis (3.8% vs. 0%), Upper respiratory tract infection (5.7% vs. 1.9%), Constipation (7.5% vs. 1.9%), Limb injury (5.7% vs. 3.8%), Oedema peripheral (15.1% vs. 9.4%), Hypertension (7.5% vs. 5.7%), Asthma (7.5% vs. 1.9%), and Insomnia (5.7% vs. 3.8%).

Severe PT more frequently reported in the Dupilumab group was only Fall (3.8% vs. 1.9%); all other severe PTs occurred individually. A reported case of severe drug-induced liver injury seemed not to be related to the study drug.

A higher proportion of study participants assigned to the dupilumab group experienced treatment-related TEAEs throughout the on-treatment period (26.4% vs. 15.1%). The difference was mainly caused by infections, such as Conjunctivitis (13.2% vs. 3.8%) and skin-related infections, further infections occurred individually. Requested analyses suggest that this observed discrepancy is rather not associated with an underlying immunosenescence of the elderly study participants.

Both deaths in the Dupilumab group occurred during the follow-up period, and after the end of study, respectively. One participant had a fatal-outcome TESAE of Cardiac failure, the other died because of a Cardiogenic shock (post-CABG surgery). Both deaths were assessed to be unrelated to the study drug.

As mentioned above, participants assigned to the placebo group experienced more TESAEs as compared to those assigned to the dupilumab group. Most TESAEs were reported in SOC Infections and infestations, however, proportions were balanced between the treatment groups without cluster.

Most TESAEs occurred individually and no TESAEs were considered related to study drug by the investigator. Similar findings were observed upon review of the exposure-adjusted incidence rates of TESAEs. As this is an elderly study population, cardiovascular events come into focus (see also analysis of AESIs by organ system below). Throughout the follow-up period, in the dupilumab group, 3 cardiac SAEs occurred, i.e. Atrial fibrillation, Cardiac failure, and Myocardial infarction, however, also in the PBO group TESAEs of Cardiovascular disorder and Coronary artery disease were reported. Reported TESAEs during the follow-up period or after end of study were without any apparent pattern and were not considered related to study drug which appears plausible based on the provided narratives.

Pre-specified AESI include Helminthic infections, COVID-19, Keratitis, Anaphylactic reactions, Systemic hypersensitivity reactions (excluding events already included under anaphylactic reaction), any severe type of conjunctivitis or blepharitis, and clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) based on (pre-)clinical data, mode of action, regulatory requirements, and epidemiological relevance. The hitherto available safety data base is extensive. Clinical data collected in elderly, however, are comparatively low as measured by all study populations, thus TEAEs that might be especially be relevant in this special population, were not (yet) defined. Overall, AESI were rarely observed. Only one event of Keratitis and Acute generalised exanthematous pustulosis were considered related to the study drug, the latter led to discontinuation of Dupilumab treatment. Regarding the analysis of AESI by organ systems, no new or unusual safety issues were identified.

As to cardiovascular and thromboembolic disorders, a more detailed analysis was conducted which is acknowledged considering age and overall health status of the studied population. During the on-treatment period a similar TEAE incidence was reported for both treatment groups, PTs that occurred in more than one participant was Cardiac failure, which was reported in 2 participants in the PBO group. There was no pattern as to observed cardiac TEAEs. No TEAEs in this SOC were considered related to study drug by the investigators and no imbalance is evident between both treatment groups.

Three participants had fatal AEs in the SOC of Cardiac disorders, 2 in the Dupilumab group and 1 on the Placebo group that were all considered by the investigator to be unrelated to study drug. The latency between last study-drug administration and death in the Dupilumab group was 56 and 67 days, respectively, and narratives do not suggest a causal relationship between the dupilumab treatment and fatal outcome.

Cardiovascular thromboembolic events were reported in 1 participant in the Placebo group (Acute myocardial infarction) and in 1 participant in the Dupilumab group (Pulmonary embolism, not related, not leading to study drug discontinuation).

Regarding the analysis of AESI by organ systems, no new or unusual safety issues were identified. Conjunctivitis is included as ADR for the BP indication which is agreed; Keratitis is mentioned in SmPC section 4.8, under 'Description of selected events' as there was a numerical imbalance between the treatment groups; however, only one event was considered related to dupilumab, and in terms of statistical calculations, the event did not qualify as an ADR in the BP population.

As elderly were, however, underrepresented throughout clinical studies compared to the overall study populations, the applicant was asked to compile a pooled analysis on the safety results in elderly across the pivotal studies leading to approval of other indications which confirmed the safety profile in elderly as compared to participants <65 years.

As to laboratory parameters, no clinically significant changes were reported for most of study participants in either of the treatment groups during the treatment period through week 52 up to data cut-off. In study R668-BP-1902, no increase in blood eosinophils was observed for most of the participants in either of the treatment groups, a phenomenon observed in AD, asthma and CRSwNP

following Dupixent treatment, in contrast, eosinophils decreased from baseline at week 4 and did not return to baseline throughout the study. This is reasoned by the standardised OCS use.

No clinically meaningful findings were reported as to physical examination or vital sign shifts from baseline.

Most study participants were aged >65 years. Infections and infestations, Skin and subcutaneous tissue disorders, Respiratory, thoracic and mediastinal disorders as well as psychiatric disorders were more frequently reported in participants aged <65 years compared with the elderly >65 years. PTs that occurred more frequently in the elderly in the Dupilumab group as opposed to the participants aged <65 years, were amongst others Pemphigoid and Pruritus. Elderly participants with BP often experience more severe symptoms which is reflected by higher incidences in Pemphigoid and Pruritus (cf. also baseline disease characteristics).

The overall incidence of treatment-emergent ADA in participants treated with dupilumab 300 mg Q2W in Study R668-BP-1902 was low, suggesting a low immunogenic potential. No participant had TEAEs potentially associated with positive ADA status.

Conjunctivitis is included as ADR for BP patients which is supported. The proposed ADR is agreed. The PI section 4.8 has been updated accordingly.

6.2. Conclusions on clinical safety

The overall safety profile seems consistent with the known Dupixent safety profile. Conjunctivitis is considered an ADR for dupilumab in patients with BP which is agreed. Apart from the higher incidence of treatment-related TEAEs Infections and infestations without specific pattern on PT level in the dupilumab 300 mg Q2W group, no new safety concerns were identified in the studied BP population in the primary analysis as well as in the updated analysis with global end of study cut-off 05 January 2025. All initial 'other concerns' were solved.

6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

7. Risk management plan

The updated European Union (EU)-RMP v12.1 is submitted to support the application for the new indication of bullous pemphigoid (BP) in adults. The RMP v12.1 incorporates updates based on the European Medicines Agency (EMA) assessment (Procedure EMA/VR/0000248778) and addresses Rapporteur feedback on the previous interim RMP v12.0 that was submitted in this process.

Significant changes to each module in version 12.1 as compared to last submitted RMP version 11.1 in Procedure number EMEA/H/C/004390/II/0083.-New indication for Chronic Spontaneous Urticaria (CSU) were the following:

Summary of significant changes in this RMP	Significant changes to each module in version 12.1 as compared to RMP version 11.1: Part I: Addition of new BP indication. Eosinophilic Esophagitis (EoE) indication text updated to reflect the European Commission Decision dated 05-Nov-2024 extending dupilumab use in pediatric patients, from 1 to 11 years of age, for EoE (procedure EMEA/H/C/004390/II/0081). Part II: Module II SI: Addition of epidemiological data for BP and update for other indications. Module II SIII: Addition of BP exposure data. Update of clinical trials cumulative exposure data and update in the number of studies for Chronic Spontaneous Urticaria (CSU) indication. Module II SIV: Addition of data relative to BP and update in number of pregnancies. Module II SV: Update of post-authorization exposure data. Module II SVII: Update of risk tables to include BP safety data. Part III: Rationale for removal of Targeted Follow-up Questionnaire Form*a*. DUPI PEDISTAD-registry-based Post-Authorization Safety Study (PASS) (CSA0014) study status update. Part V: Update in summary table indicating Targeted Follow-up Questionnaire Form removal. Update for consistency with product label. Part VI: Update for consistency with changes in other modules. Annex 2: Update for consistency with Part III. Annex 4: Removed Targeted Follow-up Questionnaire Form.

Targeted Follow-up Questionnaire Form removed based on guidance in Pharmacovigilance Risk Assessment Committee (PRAC) Guideline on specific adverse reaction follow-up questionnaires; EMA/PRAC/490455/2023 dated 28-Nov-2024 and in effect since 01-Feb-2025.

BP: Bullous Pemphigoid; CSU: Chronic Spontaneous Urticaria; EMA: European Medicines Agency; EoE: Eosinophilic Esophagitis; EU: European Union; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan.

Part II SVIII: Summary of safety concerns remains unchanged.

Summary of the safety concerns

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women
	Long-term safety in paediatric patients

Part III:

The MAH proposed to remove the hypersensitivity questionnaire for systemic hypersensitivity (including events associated with immunogenicity) which is in place to collect data from healthcare professionals for hypersensitivity events received in postmarketing setting and to detect any modifications in the risk characterization. In response to the PRAC rapporteur's comment (Procedure EMA/VR/0000248778), the applicant has referred to the Guideline on Specific adverse reaction follow-up questionnaires (EMA/PRAC/490455/2023, effective February 2025) and reviewed the continued necessity of the targeted follow-up questionnaire for hypersensitivity as part of routine pharmacovigilance activities. Based on ongoing review of post-market data, the MAH considers the important identified risk of hypersensitivity to be adequately characterized and therefore proposes removal of the targeted follow-up questionnaire. The MAH will continue other routine pharmacovigilance activities including adverse reactions reporting and signal detection. The relevant sections of the updated RMP (version 12.1) have been revised accordingly.

In the PRAC Rapporteur's opinion, the MAH's discussion on this topic is concise and it does not take into account the Section 6 of the Guidance advising that discontinuation and removal of specific AR FUQ should be considered by assessing regularly the effectiveness of the Specific AR FUQs, using process and outcome indicators and '*Discontinuation and removal of a Specific AR FUQ should be regularly considered within any procedural framework (e.g. PSUR, RMP update) in light of effectiveness results and/or the characterisation of the safety concerns over time'.*

The MAH has not presented effectiveness results either no changes emerged in the characterisation of the safety concern over time.

However, product-specific FUQs defined in the RMP may be replaced by a more generic FUQs, in those cases where FUQs are seen necessary. EMA-templates should be used when available. Attaching those in the RMP is not necessary. The MAH's proposal to remove the Hypersensitivity FUQ from the RMP is accepted but f-up data should still be collected with suitable means, using a FUQ if justified.

'Analysis of systemic hypersensitivity events in ongoing clinical studies: To detect any modifications in the risk characterization' is stated under routine PhV measures in section III.1 of the RMP and this should be added in the Table 67 in the section V.3 in the next update.

Part V:

See above. 'Analysis of systemic hypersensitivity events in ongoing clinical studies: To detect any modifications in the risk characterization' is stated under routine Phv measures in section III.1 of the RMP and this should be added in the Table 67 in the section V.3 in the next update.

Part VI:

The RMP summary was updated for consistency with changes in other modules and is considered acceptable.

7.1. Overall conclusion on the RMP

☒The changes to the RMP in v 12.1 are acceptable.

The MAH's proposal to remove the Hypersensitivity FUQ from the RMP is accepted but f-up data should still be collected with suitable means, using a FUQ if justified.

'Analysis of systemic hypersensitivity events in ongoing clinical studies: To detect any modifications in the risk characterization' is stated under routine Phv measures in section III.1 of the RMP and this should be added in the Table 67 in the section V.3 in the next update.

8. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are being updated to include aspects relevant for the BP indication. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

8.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable:

The PIL for the 300 mg PFS and PFP have only been updated to add the new BP indication. None of the changes affect the instructions for use. The consultation already performed for the previously approved indications is considered sufficient.

9. Benefit-Risk Balance

9.1. Therapeutic Context

9.1.1. Disease or condition

BP is a rare, autoimmune blistering disease primarily affecting the elderly. The disease is characterized by large, tense, serous, or hemorrhagic bullae arising on erythematous, urticarial, or eczematous skin together with the presence of itch. Lesions that involve the oral, esophageal or genital mucosa can also develop but are less common. The severity of itch, physical discomfort and pain significantly disturbs the quality of life in affected patients. The disease has a high disease burden, morbidity, and mortality due to associated infectious, cardiovascular, and neuropsychiatric comorbidities. The disease presents with a chronic relapsing course that may last from months to several years.

9.1.2. Available therapies and unmet medical need

There are no approved biologic treatments in the EU while systemic corticosteroids are approved in some member countries.

Current treatment guidelines recommend treating BP initially with oral or topical corticosteroids with the aim to achieve disease control . Doxycycline or dapsone have also been utilized in conjunction with corticosteroids as steroid sparing agents. Broad systemic immunosuppressive agents (eg, mycophenolate mofetil, methotrexate, cyclophosphamide) or off-label biologics (eg, rituximab, omalizumab) are sometimes added in patients responding poorly to OCS, or in recalcitrant patients with relapsing disease.

The prolonged use of high dose systemic or topical corticosteroid therapy is not recommended given the comorbid elderly patient population and the significant side effects associated with long-term corticosteroid use. Corticosteroids are therefore tapered expeditiously to the minimal effective dose that can control the disease. BP relapses are however frequent especially when corticosteroids are being tapered or while being weaned off corticosteroids completely. The relapse rate of BP ranges from 27.87% to 53% after disease remission, while the majority of relapses occur early (within 6 months) during remission.

An unmet medical need exists for new treatment options to control disease activity, to reduce skin and pruritic symptoms and to achieve long-term remission while minimizing the need for additional corticosteroid or other immunosuppressive treatments.

9.1.3. Main clinical studies

Data for clinical efficacy and safety are based on the single pivotal randomized, double-blind, placebo-controlled, study R668-BP-1902. The study included a 52-week double-blind treatment period and enrolled adult participants with moderate-to-severe BP (BPDAI score ≥24; measuring the extent of skin/mucosal BP involvement) and active pruritus (peak pruritus NRS ≥4). Patients received either dupilumab 300 mg SC, Q2W (including a loading dose of 600 mg) or placebo.

At baseline, all patients started treatment with a pre-defined regimen of oral corticosteroids depending on disease severity (moderate: 0.5 mg/kg/day; severe: 0.75 mg/kg/day) with the aim to achieve rapid disease control. Once stable disease control had been achieved during the first 6 weeks of treatment,

oral corticosteroids were tapered with the objective to taper them off no later than by Week 16 as long as disease control was maintained. Patients who experienced a disease relapse during or after the taper could be rescued with oral or topical corticosteroids, non-steroidal immunosuppressive medications or biologics as per investigator's discretion. Participants were allowed to continue study treatment if oral or topical corticosteroids were used.

9.2. Favourable effects

The proportion of participants achieving the primary endpoint of "sustained remission" at week 36 was (18.3%; n=9) in the dupilumab group and (6.1%; n=3) in the placebo group (95% CI: -0.79, 26.10; p=0.0645).

Numerically, the LS mean percent change from baseline in the total BPDAI activity score at week 36 was -88.5% in the dupilumab group and -73.6% in the placebo group. Patients achieving a ≥90 % reduction in BPDAI were numerically higher in the dupilumab group (75.0% vs 53.0%).

A similar numerical effect was also observed for pruritus symptoms. A total of 71.7% of patients in the dupilumab group had a reduction in the weekly average of daily peak pruritus NRS score ≥4 at week 36 as compared to 54.1% in the placebo group.

A nominal lower total cumulative OCS dose in the dupilumab group (3385.91 mg) as compared to placebo (4181.54 mg), with a mean difference of -795.63 mg at week 36 (using a treatment policy strategy for non-OCS rescue medication use) was observed.

9.3. Uncertainties and limitations about favourable effects

The primary endpoint was not met and the study failed to demonstrate its main objective. Given the applied multiple testing approach all study endpoints do not show statistically significant results. All results can only be regarded as descriptive and are not statistically confirmative. The robustness of data is largely impaired.

There are strong uncertainties on the overall data reliability given initially trigger by GCP issues leading to revisions for 2 responders for the primary endpoint. It is overall uncertain whether the study was adequately supervised and whether there are additional data issues for other study participants in other sites.

The treatment effect for the secondary endpoints is moderate with high uncertainty in point estimates.

The results for secondary endpoints are not sufficient for demonstration of efficacy and to compensate for the missed primary endpoint.

Favourable effects are based on a single pivotal study only. There is no confirmation from a second controlled study.

9.4. Unfavourable effects

The percentage of participants who reported at least 1 TEAE in study R668-BP-1902 was identical in both treatment groups (96.2%). The most frequently reported TEAE by SOC (≥5%) in the dupilumab group compared to the placebo group were Infections and Infestations (52.8% vs. 50.9%),, Gastrointestinal disorders (35.8% vs. 32.1%), Injury, Poisoning and procedural complications (32.1% vs. 28.3%), and Musculoskeletal and connective tissue disorders (32.1% vs. 20.8%).

The most frequently reported TEAEs by PT in the dupilumab group (≥5%) as compared to placebo were Conjunctivitis (7.5% vs. 0%), Constipation (7.5% vs. 1.9%), Oedema peripheral (15.1% vs. 9.4%), Vision blurred 7.5% vs. 0%), and Asthma (7.5% vs. 1.9%).

Fatal outcome TEAEs were reported for 1 participant in the placebo group and 0 participants in the dupilumab group during the on-treatment period through week 52 up to data cut-off. Fatal outcome events with an onset of the (TE)AE event after the end of the on-treatment period were reported for additional 7 participants (5 in the placebo and 2 in the dupilumab group). 5 participants experienced TEAEs with onset in the follow-up period and 2 with an AE onset after end of study.

Other SAEs were reported in a higher proportion of participants in the placebo group than in the dupilumab group (30.2% vs. 22.6%). The TE-SAE (PTs) reported in more than 1 participant were Pneumonia (PBO 0, DUP 2), Cellulitis (PBO 2, DUP 0), and Pemphigoid (PBO 2, DUP 0).

AESI were reported in a higher proportion of participants in the dupilumab group compared to the placebo group (7.5% vs. 0%). TE-AESI by SOC were 2 events of Keratitis, 1 event of Anaphylactic reaction and 1 event of Systemic hypersensitivity reaction.

Severe TEAE occurred in 22.6% of the participants assigned to the placebo group versus 17.0%of the participants in the dupilumab group.

TEAEs that were considered related to the study drug were more frequently reported in the dupilumab group than in the placebo group (26.4% vs. 15.1%). The difference between treatment groups was predominantly driven by the reporting of events in the SOC of Infections and infestations (placebo: 3.8% vs. dupilumab: 13.2%). Apart from PT Conjunctivitis, no individual PTs in the SOC of Infections and infestations were reported in >1 participant.

The incidence of ADA was overall low without relevant impact on the safety.

Results observed until global end of study in January 2025 were consistent with the primary analysis.

9.5. Uncertainties and limitations about unfavourable effects

The overall proportions of participants experiencing TEAEs were balanced across the treatment groups of the study. The majority of the observed common TEAEs were mild to moderate in severity, not related to the study intervention, and self-limiting or resolved with corrective treatment. The reported TEAEs were qualitatively consistent with those reported in previous clinical studies in adults. As to study populations included in the several clinical development programmes of other indications it should, however, be noted that elderly in general were rather underrepresented, thus, the safety data base in this special population is not so extensive compared to the general adult study population aged <65 years.

TEAEs that were considered related to the study drug were more frequently reported in the dupilumab group (26.4% vs. 15.1%) and this was mainly driven by a higher incidence in Infections and infestations. This could be explained by the immunosenescence of the elderly study participants who constitute the majority of the study population. No cluster of PTs in this SOC is present except for Conjunctivitis, a known ADR of Dupixent which is also included as ADR for the BP indication. Bearing in mind the limited participant number and comparison group, this safety finding has been included in the SmPC section 4.8.

Deaths were more frequently reported in the placebo group compared to the dupilumab group. No TEAEs leading to a fatal outcome were considered related to the study treatment.

Other SAEs were reported in a higher proportion of participants in the placebo group and no treatment-related SAE was recorded.

The severe TEAEs (PTs) reported in more than 1 participant with a higher incidence in the dupilumab group was Fall.

The immunogenic potential of dupilumab remains low.

No new safety concerns were identified in the addendum to the Primary Analysis CSR.

9.6. Effects Table

Table 52. Effects Table for Dupixent in Bullous Pemphigoid (data cut-off: 18 Feb 2025).

Effect	Short description	Unit	Treat DUPI 300mg Q2W[1,2]	Ctrl PBO[2]	Uncertainties / Strength of evidence	References
Favourable Effects						
Sustained remission	Composite endpoint: Patients with complete remission off OCS no later than Week 16 with absence of disease relapse and absence of rescue therapy until Week 36	%	18.3	6.1	Statistically not significant. Very stringent endpoint achieved only in a limited number of dupilumab-treated patients.	R668-BP-1902
Reduced disease activity	Participants achieving a ≥90% Reduction in BPDAI Activity from baseline at Week 36	%	75.0	53.0	Patients achieving complete or partial remission. Treatment policy analysis Nominal p value Large uncertainty in point estimates (95%CI: 3.16%, 39.52%)	
Reduced pruritus	Participants with improvement of Weekly Average of Daily Peak Pruritus NRS ≥4 from baseline to Week 36	%	71.7	54.1	Treatment policy analysis Nominal p value (not significant) Moderate effect Large uncertainty in point estimates (95%CI: -1.62%, 35.62%)	
Less OCS use	Total Cumulative Dose of OCS[2] from Baseline to Week 36	g	3.39	4.18	Treatment policy analysis Nominal p value (95%CI: -1234.844, -356.412)	
	To Week 52		3.70	4.89	Steroid-sparing effect of ~1g over one year	

Effect	Short description	Unit	Treat DUPI 300mg Q2W[1,2]	Ctrl PBO[2]	Uncertainties / Strength of evidence	References
Unfavourable Effects						
TE-AE treatment-related	Infections and Infestations	%	13.2	3.8	Assessed as causal relationship to study treatment	R668-BP-1902
AESI	Conjunctivitis	%	7.5	0	Listed as ADR for BP due to imbalance and clinical experience in comparison group (indications AD, asthma, CRSwNP)	idem
TE-SAE		%	22.6	30.2	RCT, incidence lower in control group	Idem
SAE with fatal outcome	On-treatment Follow-up After End-of-study	%	0 1.9 1.9	1.9 7.6 1.9	RCT Not related to study intervention	Idem
Immunogenicity	ADA response persistent	%	3.8	0	RCT	
	ADA response neutralising	%	0	0		

Abbreviations: ADA: antidrug antibodies, ADR: adverse drug reaction, AE: adverse event, AESI: adverse event of special interest BP: Bullous Pemphigoid, BPDAI: Bullous Pemphigoid Disease Activity Index, DUPI: Dupilumab, g: gram, HLT: High level term, NRS: Numerical Rating Scale, OCS: oral corticosteroids, PBO: placebo, PT: Preferred term, Q2W: biweekly, RCT: randomized controlled trial; SAE: serious adverse events, TE: treatment-emergent, SAE: serious adverse event.

Notes: [1]initial loading dose: 600mg [2]all participants were started on OCS at randomization with taper beginning by week 6 with the objective to taper off by week 16. Patients were allowed to continue treatment when rescued with oral or topical corticosteroids.

9.7. Benefit-risk assessment and discussion

9.7.1. Importance of favourable and unfavourable effects

BP is chronic relapsing disease primarily occurring in the elderly population which is associated with substantial morbidity and mortality. Current treatments mainly rely on the use of systemic or topical corticosteroids to control disease symptoms.

In the single pivotal study, no statistically significant difference in the proportion of patients achieving the primary endpoint of "sustained remission" was demonstrated. A numerical difference was observed and the overall number of responders was low in both groups (18.3%; n=9 vs. 6.1%; n=3). The initial assumption that dupilumab could lead to a very favourable clinical outcome (complete remission without the need of any additional BP-directed therapies) in a large number of patients was not achieved. In fact, complete or partial disease remissions together with reductions in pruritus symptoms were often only achieved together with additional oral or topical corticosteroid treatment as part of the allowed rescue medication. Still, dupilumab-treated patients had an overall less use of oral and/or topical corticosteroids and a clinically relevant steroid-sparing effect that translates in a difference of approximately 5 mg in daily oral corticosteroid dosing is suggested by the data.

Overall, the results suggest that a better clinical outcome (ie. improvements in skin disease activity and pruritus) with less corticosteroid use may be achieved with dupilumab. Due to the missed primary endpoint and the applied multiplicity testing strategy this data can however only be regarded as descriptive and not statistically confirmatory. Moreover, the treatment effect is rather moderate and can only be estimated with high uncertainty (large CIs). Overall the robustness of these results is very limited. In addition, next to the poor data robustness there are major uncertainties with data reliability for all study data that could not be resolved with MAHs response. The identified GCP issues as well as the provided explanations suggest a poor study oversight and it remains uncertain whether the study was adequately supervised. Given all this, the results of the secondary endpoints are not sufficient to show a treatment effect in BP and to compensate for the failed primary endpoint. Being based on data from the single pivotal trial only, efficacy has not been sufficiently demonstrated and the extension of indication cannot be accepted (**MO**).

As an immunomodulatory drug with subcutaneous route of administration, the most relevant safety concerns associated with dupilumab treatment are hypersensitivity reactions, (helminthic) infections, an increased risk for malignancy and immunogenicity as well as effects on the immature system in children. In study R668-BP-1902, there was one event of anaphylactic reaction reported in the dupilumab group, however, it was considered not related to the study drug. Another systemic hypersensitivity reaction of the skin was considered related to dupilumab. Participants who experienced TEAEs of infections were balanced across the treatment groups and no helminthic infections were reported. However, treatment-related adverse events were imbalanced between dupilumab and placebo which requires further investigation in this special population. The observed treatment-emergent adverse events were predominantly mild to moderate and resolved without additional treatment. Conjunctivitis events were imbalanced, it is therefore concurred that Conjunctivitis is included as ADR in the SmPC, however, Keratitis should also be added as ADR. The available immunogenicity data do not raise concerns and suggest a low immunogenic potential. No events of malignancy or clinically symptomatic eosinophilia were reported. The safety profile of dupilumab as already known for other indications seems to remain unaltered for the BP population. The safety profile in elderly seems to be consistent with that in study participants <65 years.

9.7.2. Balance of benefits and risks

The therapeutic need of dupilumab in BP patients with moderate-to-severe BP is acknowledged. However, the provided results from the single pivotal trial do not sufficiently demonstrate that efficacy has been established in the sought indication. The safety data appear consistent with the hitherto known safety profile bearing in mind the limited exposure due to the total small sample size.

9.7.3. Additional considerations on the benefit-risk balance

9.8. Conclusions

The overall B/R of Dupixent in the treatment of adults with moderate-to-severe bullous pemphigoid (BP) is negative.