



# Study Design of a Phase 2/3 Randomized Controlled Trial of Dupilumab in Adults with Bullous Pemphigoid: LIBERTY-BP ADEPT

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## ABSTRACT

**Background:** Bullous pemphigoid (BP) is a rare, autoimmune, blistering skin disease associated with high disease burden, profoundly decreased quality of life and increased morbidity. Emerging evidence supports an important role for type 2 inflammation in disease pathogenesis.

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Current management relies on topical and/or systemic corticosteroids, non-selective immunosuppressants and antibiotics with anti-inflammatory properties, which are all limited by side effects and toxicities. Therefore, targeted, efficacious and safe therapies are needed. Dupilumab blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation. Several reports of patients successfully treated with dupilumab have been published; however,

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dupilumab has not been formally assessed in a double-blind, placebo-controlled trial.

**Objectives:** We report the design of LIBERTY-BP ADEPT, a multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of dupilumab in adults with BP.

**Methods:** LIBERTY-BP ADEPT comprises a 35-day screening, 52-week treatment and 12-week follow-up period. Approximately 98 adults aged 18–90 years with moderate-to-severe BP are being enrolled at 51 sites on 4 continents and randomized 1:1 to subcutaneous dupilumab or placebo every 2 weeks. All participants will receive concomitant oral corticosteroids (OCS).

**Planned Outcomes:** The primary endpoint is the proportion of patients achieving complete remission off steroid therapy at week 36. Key secondary endpoints include total cumulative OCS dose to week 36, percent change and proportion of patients with  $\geq 4$ -point reduction in the weekly average of daily Peak Pruritus Numerical Rating Scale from baseline to week 36 and percent change in Bullous Pemphigoid Area Index score from baseline to week 36.

**Conclusion:** The trial results will provide evidence on whether the efficacy and safety of dupilumab support its use as a potential novel treatment approach for BP and will provide new insights into the role of type 2 inflammation in BP pathogenesis.

**Clinical Trial Registration:** ClinicalTrials.gov identifier NCT04206553.

**Keywords:** Autoimmune blistering disorder; Bullous pemphigoid; Dupilumab; Oral corticosteroids

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## Key Summary Points

Dupilumab is a fully human monoclonal antibody that inhibits the activity of both interleukin (IL)-4 and IL-13, which play a key role in type 2 inflammation in multiple diseases, including bullous pemphigoid (BP)

In recent case report studies, dupilumab successfully treated patients with recalcitrant moderate-to-severe BP

LIBERTY-BP ADEPT (NCT04206553) is an ongoing, randomized, phase 2/3 clinical trial designed to assess the efficacy and safety of dupilumab in patients with moderate-to-severe BP

LIBERTY-BP ADEPT will enroll approximately 98 patients from 51 global sites in 4 continents (North America, Europe, Australia and Asia)

## INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune skin-blistering disease. BP is associated with autoantibodies directed against the hemidesmosome transmembrane BP180 and/or intracellular BP230 proteins, which are responsible for adhesion and integrity of the dermal-epidermal junction [1]. The disease incidence varies globally, with a recent meta-analysis estimating a global incidence of 8.2–13.3 per million people [2]. The incidence has reportedly increased in the past 2 decades, likely because of an aging population and the availability of more sensitive diagnostic methods [3]. A growing amount of evidence also suggests that a number of therapies can increase the risk of developing BP and a greater use of these therapies in recent years may contribute to the rising incidence of BP [3]. A recent systematic review identified 89 drugs linked to drug-associated BP, the most common of which included gliptins,

programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors, loop diuretics and penicillin [4]. Other external factors that have been linked to the development or exacerbation of BP include radiotherapy, ultraviolet irradiation, burns (including thermal, chemical, or electrical burns), surgery, trauma, transplants and infections [5, 6].

BP predominantly affects the elderly population, with typical onset at > 70 years of age, and it often has a long disease course of months or years [7–9]. It characteristically clinically manifests with tense blisters over urticarial plaques, usually located on the trunk and limbs, accompanied by severe pruritus [1, 10, 11]. Patients with BP experience severely reduced quality of life due to intense itching and skin pain, sleep deprivation and lesions, which have a negative impact on their self-confidence, self-image and social activities [11–13]. BP can be life-threatening for elderly patients with associated comorbidities [1, 14–16], and its current management (which includes the use of non-selective immunosuppressants) poses safety concerns, including increased risk of infections and side effects and/or complications from polypharmacy. Concomitant diabetes and heart disease, which are common in the elderly, are specifically linked to increased mortality in patients with BP [16].

The mechanisms underpinning BP development are not completely understood. However, mounting evidence indicates that a type 2 inflammatory response may play a key role in disease development. Studies demonstrate elevated levels of the type 2 cytokines interleukin [IL]-4, IL-5 and IL-13, elevated levels of the chemokine eotaxin-1 and greater numbers of eosinophils in BP lesions and peripheral blood as well as increased serum immunoglobulin E (IgE) in patients with BP [17]. In addition, serum levels of anti-BP180 IgE were shown to correlate with the extent of affected body area [18]. Cells producing IL-4 and IL-13 are observed at a greater frequency in blister fluid than in the peripheral blood of patients with BP [19]. A potential role for type 2 inflammation in the disease pathogenesis of BP is also supported by the clinical characteristics of pruritus in BP, which resembles in intensity and frequency

that seen in highly pruritic Th2-response diseases such as prurigo nodularis (PN), atopic dermatitis (AD) and chronic spontaneous urticaria (CSU) [20], where dupilumab has shown benefit. Therefore, inhibiting the type 2 inflammatory pathway is a potential therapeutic target for BP.

Currently, there are no approved drugs for BP in the US; oral corticosteroids (OCS) are approved in some countries in the European Union, and human immunoglobulin is approved in Japan for BP inadequately controlled with corticosteroids. Topical corticosteroids (TCS) are commonly indicated as first-line treatment [10, 21, 22], with variable results depending on the extent and severity of the lesions. A Cochrane Review of the evidence-based literature found that potent TCS are effective in treating BP with minimal size effects, but there are significant practical barriers associated with this treatment, including the difficulty of applying TCS to large areas of skin and a potentially greater financial cost of the treatment itself (relative to OCS) as well as the potential cost of nursing care that may be required to assist in TCS application [23]. Additionally, TCS application for extensive lesions, especially in elderly patients, is difficult to manage and carries the risk of adverse effects because of systemic absorption. Moreover, chronic use of TCS is associated with skin atrophy and increased risk of infections [23]. OCS are considered the mainstay treatment for patients with BP and are first line in certain regions; however, their use is time-limited and associated with relapses and increased mortality with long-term use [22].

Off-label non-steroid immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil) and antibiotics with anti-inflammatory properties (tetracycline, sulfone) are used as adjuvant steroid-sparing therapy or independently when OCS are contraindicated; all are associated with various toxicities, including renal, mucocutaneous, pulmonary, hematologic and neurologic [10, 24–27]. Among targeted BP therapies, anti-B cell rituximab and anti-IgE omalizumab monoclonal antibodies, used off-label, were reported to achieve variable degrees of disease control in several case series

[28–30]; however, their efficacy and safety in BP have not been assessed in randomized trials.

Dupilumab, a fully human VelocImmune®-derived monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases [31–33]. Dupilumab has been shown to decrease the type 2 inflammatory biomarkers IgE, thymus and activation-regulated chemokine, eotaxin-3 and periostin in specific diseases, including AD, PN, asthma, chronic rhinosinusitis with nasal polyposis and eosinophilic esophagitis (EoE) [34]. In multiple studies, dupilumab has demonstrated rapid, significant and clinically meaningful improvement of type 2 inflammation, pruritus and skin lesions in AD and PN [35–37]. In patients with AD, it was shown that dupilumab also reduced total and allergen-specific IgE [38, 39]. In patients with CSU, dupilumab significantly and clinically improved CSU symptoms, including severe itch [40]. In two independent randomized trials in adults and adolescents with EoE, dupilumab reduced tissue eosinophils and improved symptoms associated with EoE [41]. Furthermore, in a population with severe corticosteroid-dependent asthma, dupilumab treatment significantly reduced the use of steroids while significantly improving lung capacity and reducing exacerbations [42].

Dupilumab safety has been extensively studied and is favorable across its approved indications, including in patients > 60 years [43, 44]. Given the findings from studies of dupilumab in other diseases (i.e., a reduction in both pruritus and eosinophils), dupilumab may be effective in BP. Consistent with this idea, recent publications report successful treatment of BP, including recalcitrant and moderate-to-severe BP, with dupilumab [17, 45–49]. Here, we report the study design and rationale of the LIBERTY-BP ADEPT (NCT04206553) randomized, placebo-controlled clinical trial, designed to investigate the efficacy and safety of dupilumab in patients with BP.

## METHODS

### Study Design

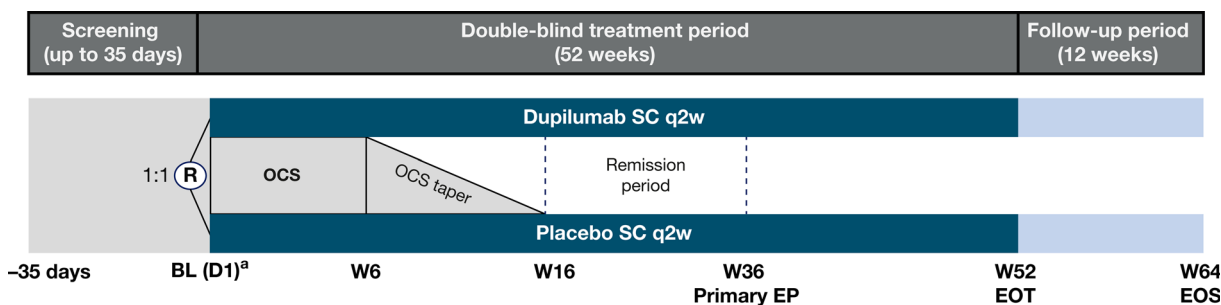
LIBERTY-BP ADEPT (NCT04206553) is a global, randomized, double-blind, placebo-controlled, parallel group, phase 2/3 study designed to assess the efficacy, safety, tolerability, pharmacokinetics and immunogenicity of dupilumab in patients with moderate-to-severe BP. The study comprises a 35-day pre-treatment screening period, a 52-week double-blind treatment period and a 12-week post-treatment follow-up period (Fig. 1). Participants included in the study will be off OCS or medium/higher potency TCS for at least 1 week before randomization.

At baseline, patients will be randomized 1:1 to subcutaneous dupilumab or placebo every 2 weeks. In parallel, all patients will receive a concomitant standard-of-care regimen of OCS (prednisone or prednisolone), which will be tapered between week 6 and week 16.

For patients who achieve complete remission off steroid therapy for at least 2 months, the interval between week 16 and week 36 will be considered the remission period, during which patients will be assessed for relapses. A relapse is defined as the appearance of at least one new eczematous lesion or urticarial plaque with diameter > 10 cm that does not heal within a week, or as the appearance of at least three smaller new lesions in the last month (blisters, eczematous lesions or urticarial plaques) [50].

### Patient Population Selection

Approximately 98 patients will be recruited at 51 global sites. At baseline, eligible patients will have confirmed histopathologic, immunopathologic and serologic diagnosis of BP; clinical BP signs (urticarial or eczematous/erythematous plaques, bullae); Bullous Pemphigoid Disease Area Index (BPDAI) activity score  $\geq 24$ ; Peak Pruritus Numerical Rating Scale (NRS) for maximum itch intensity  $\geq 4$ ; Karnofsky Performance Status Scale score  $\geq 50\%$ . Patients with other pemphigoid diseases, systemic or parasitic infections, BP secondary to medications or



**Fig. 1** Design of the LIBERTY-BP ADEPT study. A diagram illustrating the LIBERTY-BP ADEPT study design comprised of a screening period (up to 35 days), a treatment period (52 weeks) and a follow-up period (12 weeks). <sup>a</sup>Dupilumab loading dose (or equivalent placebo

dose) given at day 1. *BL* baseline, *D1* day 1, *EOS* end of study, *EOT* end of treatment, *EP* endpoint, *OCS* oral corticosteroids, *q2w* every 2 weeks, *R* randomization, *SC* subcutaneous, *W* week

severe concomitant illnesses will be excluded at screening. Detailed inclusion and exclusion criteria are presented in Table 1.

**Planned Outcomes**

The primary endpoint is the proportion of patients achieving sustained remission at week 36. Sustained remission is defined by concomitant achievement of complete tapering off OCS and complete remission (no new lesions and epithelialization of old lesions) by week 16, no relapse by week 36 and no rescue treatments by week 36.

Key secondary endpoints include total cumulative dose of OCS from baseline to week 36; percent change in weekly average of daily Peak Pruritus NRS from baseline to week 36; proportion of patients with improvement (reduction) in weekly average of daily Peak Pruritus NRS  $\geq 4$  from baseline to week 36; percent change in BPDAl score from baseline to week 36.

Other secondary endpoints at week 36 and week 52 address additional disease activity signs and symptoms, patient-reported outcomes and changes in BP180/BP230 IgG titers from baseline. Clinical pharmacology and immunogenicity endpoints include serum concentration of dupilumab over time and incidence of treatment-emergent antidrug antibodies and titers from baseline up to week 64 (end of study).

**Assessment Scales**

Peak Pruritus NRS is a patient-reported outcome of the maximum itch intensity on a scale from 0 (“no itch”) to 10 (“worst itch imaginable”). Patients will be asked to record a daily maximum score; the weekly average of daily scores will be used to assess efficacy. Peak Pruritus NRS is widely used in clinical trials to assess itch intensity in chronic pruritus [51] and is validated in other pruritic dermatoses, such as AD, with a threshold of clinically meaningful reduction of  $\geq 2$ –4 points [52].

BPDAl is a validated instrument in BP [53, 54], with a total score, which includes skin activity and mucosal activity, ranging from 0 to 360. Total BPDAl is calculated as the sum of scores for cutaneous blisters/erosions, cutaneous urticaria/erythema and mucosal blisters/erosions (each ranging from 0 to 120). Higher scores indicate higher disease activity. The minimal clinically important difference for BPDAl activity score is a 4-point reduction for assessing improvement and a 3-point increase for assessing deterioration [53].

The Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire is a 17-item validated quality of life instrument, which has demonstrated responsiveness in BP in multiple cultures and languages [55–62].

**Table 1** Key inclusion and exclusion criteria of the LIBERTY-BP ADEPT study

Key inclusion criteria	Key exclusion criteria
<ul style="list-style-type: none"> <li>• A Karnofsky Performance Status Scale score <math>\geq</math> 50% at screening</li> <li>• Baseline Peak Pruritus NRS score for maximum itch intensity <math>\geq</math> 4 (based on the average of daily NRS scores for maximum itch intensity during the 7 days before randomization)</li> <li>• A BPDAI activity score <math>\geq</math> 24 at baseline and screening visits</li> <li>• Clinical features of BP with a confirmed diagnosis based on histopathology, immunopathology and serology</li> <li>• Aged between 18 and 90 years (aged 20–90 years for study sites in Japan)</li> </ul>	<ul style="list-style-type: none"> <li>• Forms of pemphigoid other than classic BP</li> <li>• Previous treatment with IL-4 or IL-13 antagonists</li> <li>• Within 7 days of baseline visit, treatment with: <ul style="list-style-type: none"> <li>– Systemic or medium-to-high potency topical corticosteroids</li> <li>– BP-directed antibiotics such as doxycycline or dapsone</li> <li>– Nicotinamide (although use of multivitamins containing nicotinamide is allowed)</li> </ul> </li> <li>• Treatment with certain BP-directed biologics after a specified washout period prior to baseline</li> <li>• History of immunosuppression or HIV</li> <li>• Severe concomitant illnesses that would adversely affect the patient's participation in the study</li> <li>• Certain laboratory abnormalities</li> </ul>

*BP* bullous pemphigoid, *BPDAI* bullous pemphigoid disease area index, *HIV* human immunodeficiency virus, *IL* interleukin, *NRS* numerical rating scale

### Data Collection

All data generated from this study will be recorded and reported in accordance with the

protocol, Good Clinical Practice (GCP) and any applicable regulatory requirement in accordance with International Council for Harmonisation (ICH) E6. All case report form data will be collected with an electronic data capture system.

### Data Analysis

A hierarchical testing procedure will be used for multiplicity control, with each endpoint sequentially tested at a two-sided significance level until the hierarchy is broken.

### Ethics

This clinical trial will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki and consistent with the ICH guidelines for GCP, the Japanese GCP and applicable regulatory requirements. All participants must sign an Informed Consent Form prior to their participation in the study, reviewed and approved by the institutional review board (IRB) and the ethics committee (EC). Any suspected unexpected serious adverse reaction during the study will be reported to the health authorities, EC, IRB and participating investigators. Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

The safety profile of dupilumab has been well established in several clinical trials across multiple indications; however, the LIBERTY-BP ADEPT study is the first primary clinical trial to be conducted in elderly patients with a severe, potentially life-threatening disease. Therefore, an additional independent data monitoring committee, composed of members who are independent from the sponsor and the study investigators, will monitor the safety of dupilumab in patients by performing formal reviews of accumulated safety data that will be blinded by treatment group.

### STRENGTHS AND LIMITATIONS

Strengths of the study include the fact that it is the first multicenter, randomized, placebo-

controlled trial to assess efficacy and safety of dupilumab as steroid-sparing treatment for moderate-to-severe BP. Additionally, the 1-year treatment duration, with dupilumab-/placebo-only exposure for 52 weeks, considers the typically prolonged disease course and allows for observation of treatment effects beyond the timing of the primary endpoint at week 36.

Limitations include the concomitant use of OCS, which limits the assessment of dupilumab in achieving disease control as monotherapy; however, the inclusion of OCS is necessary, as patients in the placebo group require some degree of treatment.

## DISCUSSION AND DISSEMINATION

BP is a severe disease of an elderly population, and therefore LIBERTY-BP-ADEPT was designed to assess the ability of dupilumab to achieve sustained remission in patients with BP, while being able to fully taper OCS. Dupilumab has shown a favorable safety profile in several clinical trials, highlighting its tolerability and positive risk-benefit profile [35–37, 41, 42, 63].

In clinical practice, the average time to cessation of corticosteroid use is an important aspect of patient management, given that prolonged OCS use is associated with toxicity and increased mortality, particularly in elderly patients [10, 22, 24]. Although the optimal duration of OCS use is unclear, experts recommend a total treatment duration of 4–12 months [21]. Even low doses of OCS may result in OCS-related adverse events such as osteoporosis, heart failure, diabetes and infections [64], highlighting the importance of minimizing OCS treatment duration. In clinical practice, the duration of continuous treatment with OCS is often much longer; a recent prospective cohort study of 2,312 patients with BP in the UK found that a substantial proportion of patients (39.7%) were continuously treated with OCS for over a year, with 14.7% of patients treated with OCS for > 3 years, 5.0% for > 5 years and 1.7% for > 10 years [65].

The aim of the LIBERTY BP-ADEPT study (i.e., to assess whether and to what extent treatment with dupilumab can sustain disease

remission once OCSs are tapered off by week 16 or earlier) is reflected in the choice of the primary and key secondary endpoints: the proportion of patients with sustained remission at week 36 (at least 20 weeks after OCS are tapered off at week 16 or sooner) and the cumulative dose of OCS from baseline to week 36. The primary endpoint in this study is quite stringent, particularly given the short timeline to achieve this endpoint relative to treatment durations commonly used in clinical practice, which are often substantially longer than 16 weeks [65].

Pruritus is an important symptom and a major factor affecting quality of life in patients with BP [1, 10, 13]. In a multicenter study, 85% of patients with BP experienced daily itch, with a mean intensity of 5.2/10 [13]. In the LIBERTY BP-ADEPT study, the key secondary endpoints of percent change in Peak Pruritus NRS from baseline at week 36 and proportion of patients with  $\geq 4$ -point improvement in Peak Pruritus NRS at week 36 will investigate the effect of dupilumab on significant and clinically meaningful itch improvement in patients with BP.

In previous studies of BP treated with standard-of-care OCS, BPDAI score reached a minimum point at week 16 (4 months) after treatment started [66]. In the LIBERTY BP-ADEPT study design, the key secondary endpoint of percent change in BPDAI score from baseline to week 36 was chosen to assess the effect of dupilumab after early OCS discontinuation on blister, urticarial and mucosal activity.

In summary, LIBERTY-BP ADEPT is a landmark trial designed to assess the efficacy and safety of dupilumab as a steroid-sparing therapy in BP and to provide insights into the role of type 2 inflammation in the disease's pathophysiology. The results of this study will be disseminated through peer-reviewed journals and dermatology congresses.

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**Data Availability.** Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

### Declarations

**Conflict of Interest.** Dédée F. Murrell is an investigator, advisory board member for Argenx, Principia Biopharma, Regeneron Pharmaceuticals Inc., Roche; investigator for AstraZeneca; co-creator of BPDAl; creator of ABQOL. Pascal Joly is a consultant for Amgen, Argenx, AstraZeneca, Innovaderm, Principia Biopharma, Roche, Sanofi-Regeneron Pharmaceuticals Inc., Thermo Fisher Scientific. Victoria P. Werth is a consultant for AbbVie, Argenx, AstraZeneca, Janssen, Kyowa Hakko Kirin, Eli Lilly, Principia Biopharma, Regeneron Pharmaceuticals Inc., Roche-Genentech; reports grants from Argenx, Roche-Genentech, Sanofi-Regeneron Pharmaceuticals Inc., Syntimmune; co-creator of BPDAl. Hideyuki Ujiie is a consultant for Argenx, Ishin Pharma. Margitta Worm reports consultancy for AbbVie, Aimmune Therapeutics, ALK-Abelló, Amgen, AstraZeneca, Boehringer Ingelheim, DBV Technologies, Kymab, LEO Pharma, Lilly, GSK, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi-Aventis. Aaron R. Mangold reports consultancy for Argenx, Boehringer Ingelheim, Bristol Myers Squibb, Clarivate, Eli Lilly, Incyte, Janssen, Kyowa Kirin, Momenta, Pfizer, PHELEC, Regeneron Pharmaceuticals Inc., Soligenix; grants from AbbVie, Akari Therapeutics, Argenx, Corbus, Eli Lilly, Elorac, Incyte, Janssen, Kyowa Kirin, Merck, Miragen, Novartis, Palvella, Pfizer, Priovant Therapeutics, Regeneron Pharmaceuticals Inc., Soligenix, Sun

Pharma, UCB; patents for Methods and Materials for Assessing and Treating Cutaneous Squamous Cell Carcinoma (provisional 63-423254), Use of oral JAKi in Lichen Planus (provisional 63/453,065), Topical Ruxolitinib in Lichen Planus (WO2022072814A1). Elena Avetisova, Jennifer Maloney, and Arsalan Shabbir are employees and shareholders of Regeneron Pharmaceuticals Inc. Elizabeth Laws and Ariane Dubost-Brama are Sanofi employees and may hold stock and/or stock options in the company. Eric Mortensen was an employee and shareholder of Regeneron Pharmaceuticals Inc. during the development of this manuscript, and currently is an employee at AstraZeneca.

**Ethical Approval.** This clinical trial will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki, and consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), the Japanese GCP, and applicable regulatory requirements. All participants must sign an informed consent form prior to their participation in the study, reviewed and approved by the institutional review board (IRB) and the ethics committee (EC). Any suspected unexpected serious adverse reaction during the study will be reported to the health authorities, EC, IRB, and participating investigators. Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. The safety profile of dupilumab has been well established in several clinical trials across multiple indications; however, the LIBERTY-BP ADEPT study is the first primary clinical trial to be conducted in elderly patients with a severe, potentially life-threatening disease. Therefore, an additional independent data monitoring committee, composed of members who are independent from the sponsor and the study investigators, will monitor the safety of dupilumab in patients by performing formal reviews of accumulated safety data that will be blinded by treatment group.

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