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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB IN PATIENTS WITH ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Compound:	Dupilumab (REGN668)
Study Name:	Investigating Treatment with Dupilumab in Patients with ABPA (LIBERTY-ABPA AIRED)
Clinical Phase:	2
Protocol Number:	R668-ABPA-1923
Protocol Version:	R668-ABPA-1923 Amendment 4
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submission, it will be given every opportunity under applicable laws to protect its commercial interests and/or its trade secrets including the opportunity to object to such disclosure and/or provide redaction proposals.

AMENDMENT HISTORY

Amendment 4

The purpose of this amendment is to modify the study phase designation.

Description of Change	Rationale	Section Changed
The study phase has been changed from phase 4 to phase 2.	[redacted]	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration
A minor editorial correction was made concerning matching visit number and study week.	The correction was made to align with the schedule of events table.	Section 9.1.1 Footnotes for the Schedule of Events Table Section 9.1.4 End of Treatment Visit

Amendment 3

The purpose of this protocol amendment is to modify the study phase, number of participants to be enrolled, study schedule, treatment period, and endpoints. These changes are due to difficulty reaching the study enrollment goal during the COVID-19 pandemic and the low prevalence of ABPA. The study has changed from phase 3 to phase 4, the primary and secondary endpoints have been changed, and the sample size has been reduced. The following table outlines the changes made to the protocol and the affected sections:

Description of Change	Rationale	Section Changed
The sample size has been reduced from 170 participants to 60 participants, and the primary endpoint has been changed. New primary endpoint: "Change from baseline in pre-bronchodilator FEV1 compared to placebo at week 24" Previous primary endpoint, which is now a secondary endpoint and no longer compared to placebo: "Annualized rate of severe	The decision to stop enrollment was made because of difficulties enrolling participants due to the COVID-19 pandemic and the low prevalence of ABPA. Nearly 60 patients had been enrolled when the decision to stop enrollment was made. A sample size of 60 participants has insufficient power to detect a difference in severe exacerbation rates between treatment and control groups but does have enough power to detect	Clinical Study Protocol Synopsis: Population – Sample Size; Objectives; Endpoints – Primary; Statistical Plan Section 2.1 Primary Objective Section 2.2 Secondary Objectives Section 3.1 Hypothesis Section 4.1.1 Primary Endpoint Section 4.1.2 Secondary Endpoints Section 6.1 Study Description and Duration

Description of Change	Rationale	Section Changed
respiratory exacerbations defined as new onset of symptoms or clinical worsening requiring systemic corticosteroid treatment for ≥3 days; for patients who are on maintenance daily systemic corticosteroids, at least doubling of the dose of systemic corticosteroids for ≥3 days (with or without antibiotic therapy if indicated) over the 52-week treatment period compared to placebo"	a change from baseline in pre-bronchodilator FEV1 after 24 weeks of treatment.	Section 7.1 Number of Patients Planned Section 8.6 Method of Treatment Assignment Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3 Primary Efficacy Analysis
The secondary endpoint "change from baseline in pre-bronchodilator FEV1 compared to placebo at week 52" has been removed, along with the corresponding secondary objective "to evaluate the effects of dupilumab on lung function in patients with ABPA."	The endpoint has been removed to avoid redundancy, as the exploratory endpoint "change from baseline in lung function parameters (pre-bronchodilator FEV1, [redacted] from baseline to weeks 4, 8, 12, 24, 36, 44, and 52" will include the same data.	Clinical Study Protocol Synopsis: Objectives; Endpoints – Secondary Section 2.2 Secondary Objectives Section 4.1.2 Secondary Endpoints

Description of Change	Rationale	Section Changed
The study treatment period has been changed from 52 weeks to at least 24 and no more than 52 weeks.	Changes in lung function between treatment groups can be adequately assessed after 24 weeks of treatment; however, some study patients will have already received 52 weeks of treatment at the time this amendment is approved. Modification of the treatment period will result in all patients who complete the treatment period being treated for a minimum of 24 weeks and a maximum of 52 weeks. This change will shorten the time to study completion while allowing for collection of endpoint data to evaluate efficacy in patients with ABPA.	Clinical Study Protocol Synopsis: Study Duration; Statistical Plan Section 3.2.1 Rationale for Study Design Section 4.1.3 Exploratory Endpoints Section 6.1 Study Description and Duration Figure 1 Section 8.2 Background Treatments Table 1 Section 9.1.1 Footnotes for Table 1 Schedule of Events Section 9.1.2 Early Termination Visit Section 9.1.4 End of Treatment Visit Section 11.4.3 Primary Efficacy Analysis
The caps for percentage of patients receiving chronic systemic corticosteroids and oral antifungals at baseline have been removed.	By decreasing the sample size, the proportion of patients already enrolled who are on chronic systemic corticosteroids or oral antifungals has changed and the caps are no longer meaningful.	Clinical Study Protocol Synopsis: Target Population – Inclusion Criteria Section 6.1 Study Description and Duration Section 7.2 Study Population Section 7.2.1 Inclusion Criteria: #4 Section 8.2 Background Treatment Section 9.2.2.4 Patient-Reported Outcome Questionnaires

Description of Change	Rationale	Section Changed
The study phase has been changed from phase 3 to phase 4.	Dupixent has market authorization for the treatment of asthma, and all patients must have asthma in addition to ABPA to be eligible for study participation. ABPA is diagnosed by the ISHAM criteria, which for this study requires asthma in addition to evidence of immediate hypersensitivity to *Aspergillus* as well as other serologic and radiologic confirmation.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration
Secondary and exploratory endpoints will no longer be analyzed compared to placebo.	The secondary and exploratory endpoints are underpowered for comparison to placebo as a result of the reduced sample size.	Clinical Study Protocol Synopsis: Endpoints – Secondary; Statistical Plan Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 11.4.3.2 Secondary Efficacy Analysis (this section has been removed in amendment 3) Section 11.4.4 Control of Multiplicity
Language regarding the safety profile of dupilumab has been updated.	New language was provided by Global Patient Safety to ensure the most up-to-date information is contained in the protocol.	Section 3.3.1 Risk/Benefit for Dupilumab
Minor clarifications and editorial corrections have been made.	For clarification and completeness	Throughout the document, including: Section 5.2 Efficacy Variables Section 7.2.2 Exclusion Criteria Section 9.2.2.4 Patient-Reported Outcome Questionnaires Section 11.4.5.1 Adverse Events Section 11.4.5.3 Treatment Exposure

Amendment 2

The purpose of this protocol amendment is to update the inclusion and exclusion criteria to address [redacted] for patients on antifungal therapy and to allow a broader population to enroll that are still within the recognized International Society for Human and Animal Mycology (ISHAM) diagnostic criteria. Provisions were also added to protect patient safety and data integrity during the COVID-19 pandemic by allowing for certain study procedures to occur at delayed time points and/or outside of the clinic environment. Other changes were made for clarification and consistency. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Rationale	Section Changed
Antifungal therapy related changes		
The inclusion and exclusion criteria were modified such that patients on antifungal therapy at screening may enroll in the study. Patients on oral antifungal therapy at baseline will be capped at 45% of the study population. Furthermore, randomization will now be stratified by oral antifungal use at screening (yes/no), in addition to the prior stratification criteria. The statistical analysis models for this study were updated accordingly.	[redacted]	Clinical Study Protocol Synopsis: Target Population, Statistical Plan Section 4.1.3 Exploratory Endpoints Section 6.1 Study Description and Duration Section 7.2 Study Population Section 7.2.1 Inclusion Criteria: #7, #10 Section 7.2.2 Exclusion Criteria: #4 Section 8.2 Background Treatments Section 8.3 Rescue treatments Section 8.6 Method of Treatment Assignment Section 8.10.2 Permitted Medications Section 9.1.1.1 Footnotes for Table 1 Schedule of Events: footnote a Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analyses Section 11.4.3.2 Secondary Efficacy Analyses
Additional changes to inclusion and exclusion criteria		
The allergic bronchopulmonary aspergillosis (ABPA) diagnostic criteria were updated to include a broader range of eosinophil counts at screening. Additionally, the inclusion criteria were modified to permit a documented historical positive test result for the presence of serum precipitating or IgG antibodies to *A fumigatus* within 12 months prior to screening.	To provide flexibility to sites and reduce the screen failure rate by broadening the entry criteria related to ABPA while still adhering to the ISHAM 2013 diagnostic criteria for ABPA.	Clinical Study Protocol Synopsis: Target Population Section 1 Introduction Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria: #2, #4, #5

Description of Change	Rationale	Section Changed
Exclusion criteria were modified to allow patients to repeat an assessment during screening and to allow for re-screening if patients screen fail for a condition which may be transient in nature (eg, abnormal lab values).	To provide flexibility to sites.	Section 7.2.2 Exclusion Criteria Section 9.1.1.1 Footnotes for Table 1 Schedule of Events: footnote e
The exclusion criterion for a positive respiratory culture for Pseudomonas or other multi-drug resistant bacteria was removed.	To broaden the population of patients able to enroll in this study. Note that this change is not anticipated to impact efficacy or safety.	Section 7.2.2 Exclusion Criteria: #8
An exclusion criterion was added to exclude participants for country-specific exclusions.	To ensure compliance with local country-specific regulations.	Clinical Study Protocol Synopsis: Target Population Section 7.2.2 Exclusion Criteria: #42
The exclusion criterion for treatment with a live vaccine was updated to be "4 weeks" prior to the baseline visit (rather than "12 weeks").	To align with the dupilumab development program standard.	Section 7.2.2 Exclusion Criteria: #27
COVID-19 pandemic related changes		
The following changes were made for the COVID-19 pandemic: • Added text to clarify general changes to study conduct in the context of the COVID-19 pandemic. • Revised Schedule of Events (SOE) to reduce in-clinic visits and allow for study drug to be shipped to patients' home. Removed sputum component of the optional immunophenotyping substudy. The exploratory endpoint examining sputum in this substudy was also removed.	To reduce the burden on patients and to protect patient safety and data integrity in the context of the COVID-19 pandemic.	Clinical Study Protocol Synopsis: Site Location(s) Section 2.3 Exploratory Objectives Section 3.3 Risk/Benefit Section 4.1.3 Exploratory Endpoints Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria: #7 Section 9.1 Schedule of Events Section 9.2.6.6 Blood Immunophenotyping Substudy (Optional) Table 1 Schedule of Events Section 9.1.1.1 Footnotes for Table 1 Schedule of Events: footnote l, m, p, and y Section 11 Statistical Plan
Other updates		
Primary estimands were added for key endpoints.	To implement concept estimands in the primary and secondary analysis approaches for the key endpoints based on ICH E9 (R1).	Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis

Description of Change	Rationale	Section Changed
Conditions for not performing [redacted] were clarified (eg, recent chest CT scan consistent with the criteria described in the imaging manual of adequate quality as assessed by the central reader). [redacted]	To reduce the burden on patients as well as radiation exposure.	Clinical Study Protocol Synopsis: Objective(s), Population, Endpoint(s) Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 7.2.1 Inclusion Criteria: #2 Section 9.1.1.1 Footnotes for Table 1 Schedule of Events: footnote j Section 9.2.2.4 Patient Reported Outcome Questionnaires
An Asthma Control Questionnaire (ACQ-5) assessment was added to the SOE for visit 24 (week 44).	To assess asthma control during the period of the study in which in-clinic visits were reduced for the COVID-19 pandemic.	Table 1 Schedule of Events
Antineutrophil cytoplasmic antibodies (ANCA) testing was added to the SOE.	To clarify that this testing should occur at screening. (ANCA was previously listed in the safety procedure section for laboratory testing at screening, but not in the SOE.)	Table 1 Schedule of Events
Minor clarifications and editorial corrections.	For clarification.	Throughout the document.

Amendment 1

The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Language was updated to remove specific mentions of the 2019 American Thoracic Society (ATS)/European Respiratory Society (ERS) spirometry guideline. Software that is compliant with the 2019 guideline has not been developed yet and is not expected to be available in the near future.	Section 9.1.1.1 Table 1 Schedule of Events, footnote d Section 9.2.2.2 Lung Function Section 19 References

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ABPA	Allergic bronchopulmonary aspergillosis
ACQ	Asthma Control Questionnaire
AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCA	Antineutrophil cytoplasmic antibodies
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BD	Bronchodilator
BUN	Blood urea nitrogen
CCL	Chemokine (C-C motif) ligand
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSR	Clinical study report
CT	Computed tomography
DMC	Data monitoring committee
EC	Ethics committee
ECG	Electrocardiogram
ED	Emergency department
EDC	Electronic data capture
EGPA	Eosinophilic granulomatous with polyangiitis
EMA	European Medicines Agency
EOE	Eosinophilic esophagitis
EOS	End of study
EOT	End of treatment
ERS	European Respiratory Society
EU	European Union
FAS	Full analysis set

FDA	Food and Drug Administration
[redacted]	[redacted]
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HU	Hounsfield units
HRQoL	Health-related quality of life
[redacted]	[redacted]
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
IL4Rα	Interleukin-4 receptor alpha
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISHAM	International Society for Human and Animal Mycology
IVRS	Interactive voice response system
IWRS	Interactive web response system
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic receptor antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist

MMRM	Mixed-effects model with repeated measures
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
OCS	Oral corticosteroids
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PK	Pharmacokinetic
Q2W	Every two weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SABA	Short-acting bronchodilators
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SGRQ	St. George's Respiratory Questionnaire
SLIT	Sublingual immunotherapy
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Allergic Bronchopulmonary Aspergillosis
Site Location(s) **Principal Investigator**	Approximately 80 to 100 sites are planned, in the United States (US), European Union (EU), and other world regions. (PI TBD)
Objective(s)	The primary objective of the study is to evaluate the efficacy of dupilumab on lung function in patients with allergic bronchopulmonary aspergillosis (ABPA). The secondary objectives of the study are: • To evaluate the effects of dupilumab on exacerbations in patients with ABPA • To evaluate the effects of dupilumab on ABPA-related exacerbations • To evaluate the effects of dupilumab on hospitalization/emergency department (ED)/urgent care visits in patients with ABPA • To evaluate the effects of dupilumab on asthma control in patients with ABPA • To evaluate the effects of dupilumab on health-related quality of life (HRQoL) in patients with ABPA • To evaluate the effects of dupilumab on serum total IgE and *Aspergillus*-specific IgE concentrations • To evaluate the effects of dupilumab on fractional exhaled nitric oxide (FeNO) levels • To evaluate safety and tolerability of dupilumab in patients with ABPA • To evaluate dupilumab concentrations in serum and the incidence of anti-dupilumab antibodies in patients with ABPA
Study Design	Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate efficacy and safety of dupilumab in patients with ABPA. The 3 study periods include a screening period, a randomized treatment period, and a post-treatment follow-up period. Patients will be randomized 1:1 to receive either dupilumab 300 mg given subcutaneously (SC) after a loading dose of 600 mg, or matching placebo given SC every 2 weeks (Q2W).
Study Duration	The study duration is 36–64 weeks, excluding the 4-week screening period. The randomized treatment period is 24–52 weeks, with all patients being treated for a minimum of 24 weeks and a maximum of 52 weeks. The post-treatment follow-up period is 12 weeks.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

Population

Sample Size: Approximately 60 patients will be enrolled.

Target Population: Adults and adolescents (≥12 years of age) with ABPA who meet modified International Society for Human and Animal Mycology (ISHAM) working group 2013 criteria for ABPA.

Main inclusion criteria

- Males and females ≥12 years of age at screening
- Diagnosis of ABPA defined by the following criteria at screening:

  Obligatory criteria at screening (must meet all 3 criteria):

  - Physician diagnosis of asthma for at least 12 months based on the Global Initiative for Asthma (GINA) 2019 guidelines
  - Evidence of sensitization to *Aspergillus fumigatus* by skin testing (at screening or documented historical positive skin test in the previous 12 months), or elevated *A fumigatus*-specific IgE in serum (≥0.35 kU/L) at screening
  - Elevated serum total IgE > 1000 IU/mL. If all 3 supportive criteria for ABPA (below) are met, IgE ≤1000 IU/mL is acceptable. If the patient is receiving oral corticosteroids (OCS) at screening, a documented historical IgE >1000 IU/mL within the previous 12 months is acceptable

  And 2 or more of the following supportive criteria

  - For patients on OCS, blood eosinophil count >500 cells/µL at screening or a documented historical blood eosinophil count >500 cells/µL within 12 months of screening. For patients not on OCS, blood eosinophil count >500 cells/µL at screening or blood eosinophil ≥300 to ≤500 cells/µL at screening with a documented historical blood eosinophil count >500 cells/µL within 12 months of screening.
  - The presence of serum precipitating or IgG antibodies to *A fumigatus* at screening or a documented historical positive test result within 12 months prior to screening.
  - Documented radiological findings consistent with ABPA (such as fleeting pulmonary parenchymal opacities, mucoid impaction, high-attenuation mucus, centrilobular nodular opacities, atelectasis, bronchiectasis, etc) by historical chest x-ray or chest computed tomography (CT) or magnetic resonance imaging (MRI) within the previous 18 months or at screening
- On a maintenance therapy for their asthma with controller medication which must include inhaled corticosteroids (ICS) and may include 1 or more additional controller medications including a long-acting beta agonist (LABA), leukotriene receptor antagonist (LTRA), and/or

long-acting muscarinic receptor antagonist (LAMA), etc for at least 12 weeks, with a stable dose and regimen with no change in the dose or frequency of administration for at least 4 weeks prior to the screening visit, and between the screening and baseline/randomization visits

- For patients on OCS: must be on a chronic stable dose (no change in the dose) of OCS of up to 10 mg/day (for patients taking daily corticosteroids) or up to 30 mg every alternate day (for patients taking alternate day corticosteroids) of OCS (prednisone/prednisolone or the equivalent) for at least 4 weeks prior to the screening visit and between the screening and the baseline/randomization visit. In addition, patients must agree to switch to study-required prednisone/prednisolone as their OCS at visit 1 and use it per protocol for the duration of the study.
- Must have experienced ≥1 severe respiratory exacerbation requiring treatment with systemic corticosteroids or hospitalization or treatment in ED/urgent care within 12 months prior to the screening visit, or must be receiving chronic stable low-dose OCS
- ACQ-5 score of ≥1.5 at screening and at baseline visit
- For patients receiving oral antifungals at baseline: must be on a stable dose and regimen of a single antifungal medication for at least 4 weeks prior to screening and between the screening and baseline visit.

Main exclusion criteria

- Weight less than 30.0 kilograms
- Current smoker or e-cigarette user, or cessation of smoking or e-cigarette use within 6 months prior to randomization, or > 10 pack-years smoking history
- Post-bronchodilator forced expiratory volume in 1 second (FEV1) < 30% predicted normal at screening
- For those receiving OCS at baseline: Considered to be at high risk for adverse events due to tapering of OCS, in the opinion of the investigator
- Respiratory exacerbation requiring systemic corticosteroids within 4 weeks prior to screening and between screening and baseline visit (for patients on daily or alternate day OCS, exacerbation requiring at least double the maintenance dose of corticosteroids)
- Upper or lower respiratory tract infection within the 4 weeks prior to screening (visit 1) or between the screening and randomization visits
- Significant chronic pulmonary disease other than asthma with ABPA (eg, physician-diagnosed bronchiectasis due to a condition other than ABPA ; cystic fibrosis; sarcoidosis; interstitial lung disease not due to ABPA; chronic obstructive pulmonary disease [COPD] not due to ABPA; hypereosinophilic syndrome; etc) or a diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts
- Diagnosis or suspected diagnosis of eosinophilic granulomatous with polyangiitis (EGPA) also called Churg-Strauss Syndrome
- Diagnosis of aspergilloma, invasive or disseminated aspergillosis, or chronic pulmonary aspergillosis

	• Any country-specific regulation that would prevent the participant from entering the study
Treatment(s)	
Study Drug	Dupilumab, as 150 mg/mL solution for SC injection.
Dose/Route/Schedule:	Loading dose of 600 mg on day 1, followed by 300 mg SC, Q2W.
Placebo Route/Schedule:	Placebo, matching dupilumab formulation without addition of protein. Administered SC, Q2W
Endpoint(s)	
Primary:	The primary endpoint is the change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) compared to placebo at week 24.
Secondary:	1. Annualized rate of severe respiratory exacerbations, defined as new onset of symptoms or clinical worsening of respiratory symptoms requiring systemic corticosteroid treatment for ≥3 consecutive days; for patients who are on maintenance systemic corticosteroids, at least double the dose of maintenance systemic corticosteroids for ≥3 consecutive days (with or without antibiotic therapy if indicated) over the 24–52-week treatment period 2. Annualized rate of ABPA-related exacerbations, defined as severe respiratory exacerbations (as defined above) that are associated with a doubling of serum total IgE from the prior pre-exacerbation value, over the 24–52-week treatment period 3. Annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility during the 24–52-week treatment period 4. Change from baseline in Asthma Control Questionnaire (ACQ-5) over the 24–52-week treatment period 5. Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over the 24–52-week treatment period 6. Percentage of participants achieving a reduction in the SGRQ score of 4 points or greater from baseline to weeks 12, 24, 36, and 52 7. Percent change from baseline in total IgE in serum over the 24–52-week treatment period 8. Percent change from baseline in *A fumigatus*-specific IgE in serum over the 24–52-week treatment period 9. Percent and absolute change from baseline in fractional exhaled nitric oxide (FeNO) over the 24–52-week treatment period 10. Incidence of treatment-emergent adverse events (TEAEs) from baseline through the end of treatment (week 24–52) 11. Immunogenicity of dupilumab, as determined by the incidence, titer, and clinical impact of treatment-emergent ADA to dupilumab over time 12. Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to the end of study
Procedures and Assessments	Efficacy procedures and assessments include: the number of severe respiratory exacerbations over the treatment period and clinical signs and symptoms of respiratory exacerbation; assessment of lung function parameters, using spirometry, such as FEV1, [redacted] number of ABPA-related exacerbations (ie, those

	associated with a doubling of serum IgE compared to the pre-exacerbation level) over the treatment period; number of severe respiratory exacerbations that are associated with hospitalization, ED, or urgent care visits; [redacted]; patient-reported outcome questionnaires (SGRQ, ACQ-5); systemic corticosteroid use; oral antifungal use and [redacted] Safety procedures include: vital signs; physical examination; electrocardiogram; laboratory testing. Samples will be collected for trough dupilumab concentrations, anti-drug antibody (ADA) and neutralizing antibody (NAb) assessment, and pharmacodynamic/biomarker assessments. Fractional exhaled nitric oxide, serum IgE, *A fumigatus*-specific IgE, [redacted] will be measured. A subset of study sites may be selected to perform evaluations of circulating immune cells before and after dupilumab treatment. Participation in future biomedical research and pharmacogenomic analysis will be optional.
Statistical Plan	The power calculation for this study is based on a comparison between dupilumab 300 mg Q2W and placebo with regard to the primary endpoint of the absolute change from baseline in pre-bronchodilator FEV1 at week 24. Assuming a randomization ratio of 1:1, a standard deviation (SD) for the change from baseline in pre-bronchodilator FEV1 at week 24 of [redacted] in both groups, a 2-sided Type 1 error of 0.05, and a dropout rate of [redacted] by week 24, with approximately 60 randomized patients (~30 patients per group), the study will have approximately 96% power to detect a difference of [redacted] in the change from baseline in pre-bronchodilator FEV1 at week 24 between the dupilumab and placebo groups, based on the 2-sample t-test. [redacted] For the primary analysis, the absolute change from baseline in pre-bronchodilator FEV1 at week 24 will be analyzed using a mixed-effects model with repeated measures (MMRM) approach. The vector of responses will consist of the absolute change from baseline in pre-bronchodilator FEV1 at weeks 2, 4, 8, 12, and 24. For patients who discontinue study treatment prior to week 24, any off-study treatment pre-bronchodilator FEV1 values collected after the discontinuation of study treatment through week 24 will be included in the analysis. The MMRM model will include OCS use at screening, OAF use at screening, region, age, sex, height, baseline eosinophil count, treatment, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV1 value, and baseline pre-bronchodilator FEV1 value-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the correlations between repeated measurements. Parameters will be estimated using the restricted maximum likelihood (REML) method and the Newton-Raphson algorithm. Statistical inference for the treatment comparison of the absolute

	change from baseline in pre-bronchodilator FEV1 at week 24 will be derived from the MMRM model using the Kenward Roger method for calculation of the denominator degrees of freedom for the tests of the fixed effects. If the model does not converge, alternative model specifications (eg, a different covariance structure or reduction in the number of covariates) will be applied; details will be provided in the SAP. For safety analysis, the summary of safety results will be presented by treatment group. All safety analyses will be performed on the safety analysis set (SAF).

1. INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a progressive, immunologic lung disease caused by hypersensitivity to the fungus *Aspergillus fumigatus* (*A fumigatus*) that occurs in patients with asthma or cystic fibrosis (Agarwal, 2014). The prevalence of ABPA is estimated to be 1% to 3% in patients with severe asthma referred for specialty care (Eaton, 2000) (Kurup, 2009). Clinically, asthma patients with ABPA have a more severe clinical course with poorly controlled asthma, poor response to treatment, and frequent episodes of exacerbations compared to patients with asthma who do not have ABPA. In addition, ABPA is often associated with thick mucoid secretions that can lead to obstruction of large and small airways, bronchiectasis (which does not otherwise occur in asthma), and lung function impairment beyond that seen in a typical asthma patient. A staging system is described for patients with asthma and ABPA to monitor disease progression clinically. Depending on the stage of the disease, clinical features in ABPA vary from mild asthma with occasional episodes of wheezing and cough, to patients with fibrosis, honeycomb lung, and respiratory failure (Patterson, 1982). Stage I is the initial acute stage of ABPA manifesting clinically with productive cough, wheeze, shortness of breath, fever, malaise, pleuritic chest pain, elevated serum immunoglobulin E (IgE), peripheral and tissue eosinophilia, and fleeting pulmonary infiltrates on imaging studies. In stage II, the disease goes into remission for a variable period; symptoms are reduced, the lung infiltrates clear, and the serum IgE value declines. Stage III is characterized by respiratory exacerbations with the recurrence of symptoms, production of thick sputum plugs, and an increase in serum total IgE levels that occur in up to 24% to 50% of patients each year (Agarwal, 2016) (Muthu, 2019). During episodes of exacerbations, thick brown mucoid sputum may contain *A fumigatus* hyphae. Stage IV is reached when, despite treatment, the disease progresses to extensive mucoid impaction of airways visible on chest x-ray or computed tomography (CT) imaging, lung function decline, and corticosteroid dependence. Stage V is the fibrotic stage. Unlike asthma, which does not progress to fibrotic lung disease, if the diagnosis is delayed or the disease is undertreated, ABPA progresses to a fibrotic end-stage lung disease that can lead to pulmonary hypertension, cor pulmonale, and respiratory failure.

The diagnosis of ABPA is based on clinical, serological, and radiological criteria. Diagnostic criteria for ABPA have evolved over the past several decades with an increased understanding of the disease, recognition of “severe asthma with fungal sensitization” as a distinct clinical entity, and improvement in serological testing. Diagnostic criteria for ABPA, modified in 2013 by the International Society for Human and Animal Mycology (ISHAM) Working Group, are widely used clinically, wherein the items are broadly divided into ‘obligatory’ and other supportive criteria (Agarwal, 2013). The obligatory diagnostic criteria include the presence of a predisposing condition (asthma or cystic fibrosis), elevated serum total IgE >1000 IU/mL, and evidence of sensitization to *A fumigatus* (either a positive immediate hypersensitivity skin test or elevated serum-specific IgE to *A fumigatus*). Supportive criteria for the diagnosis include 2 of the following 3 criteria: 1) eosinophilia >500 cells/µL in steroid naïve patients (may be historical); 2) serum precipitating or IgG antibodies to *A fumigatus*; and 3) radiographic findings consistent with ABPA.

Approximately 20% to 30% of asthma patients are sensitized to *A fumigatus* (Eaton, 2000) (Schwartz, 1978); however, only a small minority of these patients develop ABPA. In individuals who develop ABPA, exposure to fungal antigens results in immune deviation toward a robust type 2 inflammatory response with release of type 2 cytokines (eg, interleukin 4 or IL-4, IL-5, IL-9, IL-13); activation of mast cells, eosinophils, and basophils; and isotype switching of lymphocytes to IgE-producing B lymphocytes and plasma cells (Knutsen, 2011) (Chauhan, 2000). Ultimately, this florid type 2 inflammatory response is deleterious, resulting in mucoid impaction of bronchi, bronchiectasis, eosinophilic inflammation, bronchocentric granulomatosis, and exudative or obliterative bronchiolitis. This type 2-skewed immune response is thought to be related to genetically determined risk factors. Human leucocyte antigen (HLA) haplotypes (HLA‑DRB1*1501 and HLA‑DRB1*1503) are associated with a high risk of developing ABPA and promote exaggerated type 2 immune responses with continued synthesis of IgE upon exposure to *A fumigatus* antigens (Chauhan, 2000). Conversely, HLA‑DQ2 (HLA‑DQB1*0201 in particular) is associated with a lower risk of ABPA (Chauhan, 2000). There are increasing numbers of reports of single nucleotide polymorphisms in host response genes (eg, polymorphisms in *IL4R, IL13, IL10, TLR3, EEA1*) found in ABPA patients, suggesting a panoply of underlying abnormalities in both adaptive and innate immunity (Knutsen, 2006a) (Overton, 2018) (Overton, 2016). Gain-of-function variants in *IL4R* are prevalent in atopic disease and lead to exaggerated synthesis of IgE antibodies and increases in the number of tissue mast cells (Hershey, 1997). Of note, a gain-of-function mutation in the extracellular coding region of *IL4R* (ile75val) was present in 80% of the ABPA patients in 1 study (Knutsen, 2006b). Studies have shown that B cells from patients with ABPA have higher sensitivity to IL‑4 and spontaneously produce larger amounts of IgE, IgG, and IgA antibodies against *A fumigatus* antigens (Hershey, 1997) (Knutsen, 1990).

The current mainstay of treatment for ABPA is administration of systemic corticosteroids, with many patients becoming corticosteroid-dependent to control the disease. However, not all patients respond to systemic corticosteroids. Long-term use of systemic corticosteroids is not recommended due to the lack of evidence supporting prevention of progressive bronchial destruction and the potential for serious side effects associated with chronic use. ABPA-complicating asthma does not respond clinically to conventional asthma therapy including high doses of inhaled corticosteroids (ICS). Various antifungal agents (eg, itraconazole, voriconazole, ketoconazole, amphotericin B) are used as adjunctive treatments for ABPA in patients who respond poorly to corticosteroids in an effort to reduce the fungal antigenic stimulus (Agbetile, 2014) (Stevens, 2000) (Agarwal, 2018). However, clinical response to antifungals is variable, antifungal therapy is not curative, and the side effects of antifungals - which include nausea, vomiting, diarrhea, fever, rash, headache, and hepatotoxicity −limit their use. Long-term studies to evaluate the effect of treatment with these agents to modify the progressive decline in lung function in ABPA are lacking.

One prior clinical trial of omalizumab (an anti-IgE monoclonal antibody) has been published (Voskamp, 2015). In this randomized crossover trial of 13 patients with ABPA and asthma, 4 months of omalizumab was associated with a reduced rate of exacerbation. The efficacy and safety of biologics that target eosinophilic or type 2 inflammation have not been established in ABPA. No biologic has been approved for the treatment of ABPA by either the Food and Drug Administration (FDA) or European Medicines Agency (EMA).

Thus, there is an unmet need for more effective and safe treatments that target the immunological underpinnings of ABPA to prevent irreversible airway and parenchymal disease, improve clinical symptoms, and obviate the need for systemic corticosteroids with their accompanying safety concerns.

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, key cytokines that drive the type 2 inflammatory response, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. Dupilumab, therefore, may have the potential to treat ABPA, a disease driven by type 2 inflammation.

Dupilumab (brand name DUPIXENT®) has been approved as an add-on maintenance treatment in patients with moderate to severe asthma aged 6 years and older with an eosinophilic phenotype or with oral corticosteroid (OCS)-dependent asthma in the United States (US), and in the European Union (EU) for severe asthma with type 2 inflammation characterized by raised blood eosinophils, and/or raised fractional exhaled nitric oxide (FeNO) in patients who are inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment. In Japan, dupilumab has been approved for patients aged ≥12 years with severe or refractory asthma whose symptoms are inadequately controlled with existing therapy. Additionally, dupilumab has been approved in over 50 countries for the treatment of patients aged ≥6 years with inadequately controlled moderate-to-severe atopic dermatitis (AD) or with severe AD who are candidates for systemic therapy. In the US, dupilumab is approved for use in pediatric patients aged ≥6 months. Dupilumab is also approved in the US and EU in adult patients with chronic rhinosinusitis with nasal polyposis (CRSwNP), and in the US in adult patients with prurigo nodularis and patients ≥12 years (and ≥40 kg) with eosinophilic esophagitis.

This study is designed to provide evidence of the efficacy and safety of dupilumab in patients with ABPA who remain uncontrolled despite ICS.

Additional background information on the study drug and dupilumab development program can be found in the Investigator's Brochure (IB).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of dupilumab on lung function in patients with ABPA.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effects of dupilumab on exacerbations in patients with ABPA
- To evaluate the effects of dupilumab on ABPA-related exacerbations
- To evaluate the effects of dupilumab on hospitalization/emergency department (ED)/urgent care visits in patients with ABPA
- To evaluate the effects of dupilumab on asthma control in patients with ABPA
- To evaluate the effects of dupilumab on health-related quality of life (HRQoL) in patients with ABPA
- To evaluate the effects of dupilumab on serum total IgE and *Aspergillus*-specific IgE concentrations
- To evaluate the effects of dupilumab on FeNO levels
- To evaluate safety and tolerability of dupilumab in patients with ABPA
- To evaluate dupilumab concentrations in serum and the incidence of anti-dupilumab antibodies in patients with ABPA

2.3. Exploratory Objectives

The exploratory objectives of the study are:

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Treatment with dupilumab will be efficacious in improving lung function and will be well tolerated in adult and adolescent patients ≥12 years of age with ABPA compared to treatment with placebo.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is designed to investigate the efficacy and safety of dupilumab in patients with ABPA.

A double-blinded, randomized trial design is chosen to minimize bias in data collection and result interpretation. The presence of a placebo arm is appropriate for the objectives of this study as this will allow for the most robust assessment of the efficacy and safety of dupilumab. Although dupilumab has been shown to be efficacious and safe to treat patients with moderate-to-severe asthma, neither the safety nor the efficacy of dupilumab for ABPA in patients who have asthma has been established. In contrast to asthma, ABPA is characterized by irreversible airway damage and parenchymal involvement, thus the known efficacy of dupilumab on key asthma outcomes cannot be easily extrapolated to ABPA. In addition, all patients will be allowed to receive rescue treatment with systemic corticosteroids (standard of care) and antifungal therapy (widely though not universally used) as necessary and will be closely monitored throughout the study. The proposed treatment duration of at least 24 and no more than 52 weeks provides an opportunity to assess the impact of dupilumab on multiple clinical outcome measures of ABPA including long-term changes in lung function; symptom control; rate of severe respiratory exacerbations; [redacted]; and pharmacodynamic (PD) effects on biomarkers of type 2 inflammation in ABPA, including serum total and *A fumigatus*-specific IgE levels. Patients will be treated for a minimum of 24 weeks and a maximum of 52 weeks. Details on the variable treatment period can be found in Section 9.1.1.

A 12-week post-treatment safety follow-up period is chosen based on the time expected for dupilumab drug levels to reach below the lower limit of quantification after the last dose of the drug.

The primary endpoint is the absolute change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) at week 24, as this is a well-accepted parameter to determine the effect of a drug on lung function. Lung function testing is useful in evaluating the progression of ABPA since decreased lung function is frequently associated with the disease. In a survey of 126 patients with ABPA, 85.7% had abnormal lung function (Agarwal, 2006). Secondary endpoints include: annualized rate of severe respiratory exacerbations; ABPA-related exacerbations (in which serum IgE doubles compared to the closest pre-exacerbation value); St. George's Respiratory Questionnaire (SGRQ), a widely used, validated questionnaire to assess the impact of the drug on HRQoL measures in chronic respiratory diseases; and the Asthma Control Questionnaire (ACQ-5), a validated measure of asthma control. Systemic drug concentration/anti-drug antibodies (ADA) and biomarkers (serum total IgE, *A fumigatus*-specific IgE, [redacted] have been used previously in the dupilumab program to evaluate the exposure/effect relationship and will help to better understand the mechanism of action of dupilumab and IL-4 receptor pathway in patients with ABPA.

3.2.2. Rationale for Dose Selection

The proposed dose for this study is dupilumab 300 mg administered subcutaneously (SC) every two weeks (Q2W) with a 600 mg loading dose for the first dose. This dose has proven to be effective and to have an acceptable safety profile in adult and adolescent patients with moderate-to-severe asthma. In addition, dupilumab 300 mg every two weeks (Q2W) has shown a significant [redacted] while significantly reducing exacerbations and improving lung function in a population of corticosteroid-dependent patients with severe asthma. This dose regimen is approved in the treatment of patients with corticosteroid-dependent asthma. Severity of asthma in ABPA is generally greater than in asthma patients without ABPA, and many ABPA patients require treatment with chronic systemic corticosteroids. Therefore, to achieve the optimal benefit-risk ratio in patients with ABPA, dupilumab 300 mg Q2W dosing regimen is selected for this study.

3.3. Risk/Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any new patients in this study unless the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. The sponsor plans to obtain approvals from health authorities/ethics committees to enable continuation of study sites for this study, as allowed by local laws and regulations.

3.3.1. Risk/Benefit for Dupilumab

Dupilumab has shown clinically relevant benefit in several type 2-mediated immune disorders including AD, bronchial asthma, CRSwNP, and eosinophilic esophagitis (EoE).

In adults and adolescents with moderate-to-severe uncontrolled asthma, dupilumab significantly reduced the risk of severe exacerbations compared to placebo and consistently improved lung function (FEV1), asthma control, and HRQoL in patients with a type 2 inflammatory signature as evidenced by a blood eosinophil count of ≥150 cells/μL or a fractional exhaled nitric oxide concentration of ≥25 parts per billion (ppb). In OCS-dependent patients with severe asthma, dupilumab significantly reduced the need for OCS by ~70% while at the same time reducing asthma exacerbations and improving FEV1 compared to placebo.

Type 2 inflammation plays a critical role in the pathogenesis of ABPA. The hypothesis that blocking key mediators of type 2 inflammation will lead to clinical benefit in patients with ABPA is supported by a post-hoc subgroup analysis from the completed dupilumab phase 3 pivotal study EFC13579 (QUEST) in patients with moderate-to-severe asthma who met the suggested criteria for ABPA diagnosis at baseline. The results from a total of 30 patients (n=18 in the combined dupilumab group and 12 in the combined placebo group) provide compelling clinical evidence for the efficacy of dupilumab in patients with ABPA. Dupilumab treatment compared to placebo showed an approximately 80% reduction in annualized severe exacerbation events and a 0.26L improvement in change from baseline to week 24 in pre-bronchodilator (BD) FEV1. In clinical practice, serum total IgE, which is elevated in patients with ABPA, is monitored to assess ABPA disease activity. Dupilumab suppressed serum total IgE by approximately 70% from baseline over a 52-week treatment period. Overall, dupilumab was well tolerated in this subgroup of patients with ABPA.

For dupilumab, the safety data observed so far in completed and currently ongoing studies have demonstrated a satisfactory safety profile. As of 28 March 2022 (data lock point of last PBRER), approximately 13,577 subjects were enrolled into the development program for dupilumab and are included in the safety population: 564 as healthy volunteers, 4998 from atopic dermatitis studies, 4195 from asthma studies, 880 from rhinosinusitis studies, 468 from eosinophilic esophagitis studies, 275 from allergy studies, 1495 from chronic obstructive pulmonary disease studies, 309 from prurigo nodularis studies, 311 from urticaria studies, 45 from bullous pemphigoid study, and 37 from an allergic bronchopulmonary aspergillosis study.

Dupilumab has demonstrated a favorable safety profile in clinical studies across all approved indications. The identified adverse drug reactions (ADRs) observed across all indications are Injection Site Reactions (ISRs), Sickness-like reaction/Serum Sickness and anaphylactic reaction. Though serious serum sickness and serum sickness-like reactions were observed rarely and only in AD clinical trials, and dupilumab-related anaphylactic reaction was observed rarely and only in an asthma clinical trial, they are considered ADRs across all indications as hypersensitivity is not expected to be indication specific. As protein therapeutics, all monoclonal antibodies are potentially immunogenic. Systemic hypersensitivity is considered an important identified risk for dupilumab.

Eosinophilia associated with clinical symptoms in asthma patients is an important potential risk, based on cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia reported in asthma clinical trials (as well as in adult patients with co-morbid asthma in the CRSwNP development program). These events may usually, but not always, be associated with the reduction of oral corticosteroid therapy. A causal association between dupilumab and these conditions has not been established In the AD clinical studies, Conjunctivitis, Conjunctivitis Allergic, Conjunctivitis Bacterial, Blepharitis, Dry Eye, Eye Pruritus, Herpes Simplex (primarily mucocutaneous in nature), Eosinophilia and Oral Herpes were identified ADRs. The eye and herpes related ADRs appear to be predominantly AD indication specific. Conjunctivitis is also considered an ADR for the CRSwNP indication, although it occurred at a lower incidence in these studies than in AD studies. Most events were mild in intensity, transient in nature, and did not necessitate treatment discontinuation. Conjunctivitis and keratitis related events in AD patients are an important identified risk for dupilumab. In the completed AD studies in children 6 to 17 years of age, the safety profile was consistent with that reported in adults and there were no new safety concerns identified. In a study in participants aged 6 to 11 years with asthma, Enterobiasis and Eosinophilia were identified as additional ADRs. Angioedema, Arthralgia, Keratitis, Ulcerative Keratitis, and Facial Rash have been identified as ADRs in the post marketing setting. The program has a data monitoring committee (DMC), which will review the benefit/risk on a regular basis. A complete efficacy and safety profile of dupilumab, with respect to the overall development program, is provided in the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint of the study is the change from baseline in pre-bronchodilator FEV1 compared to placebo at week 24.

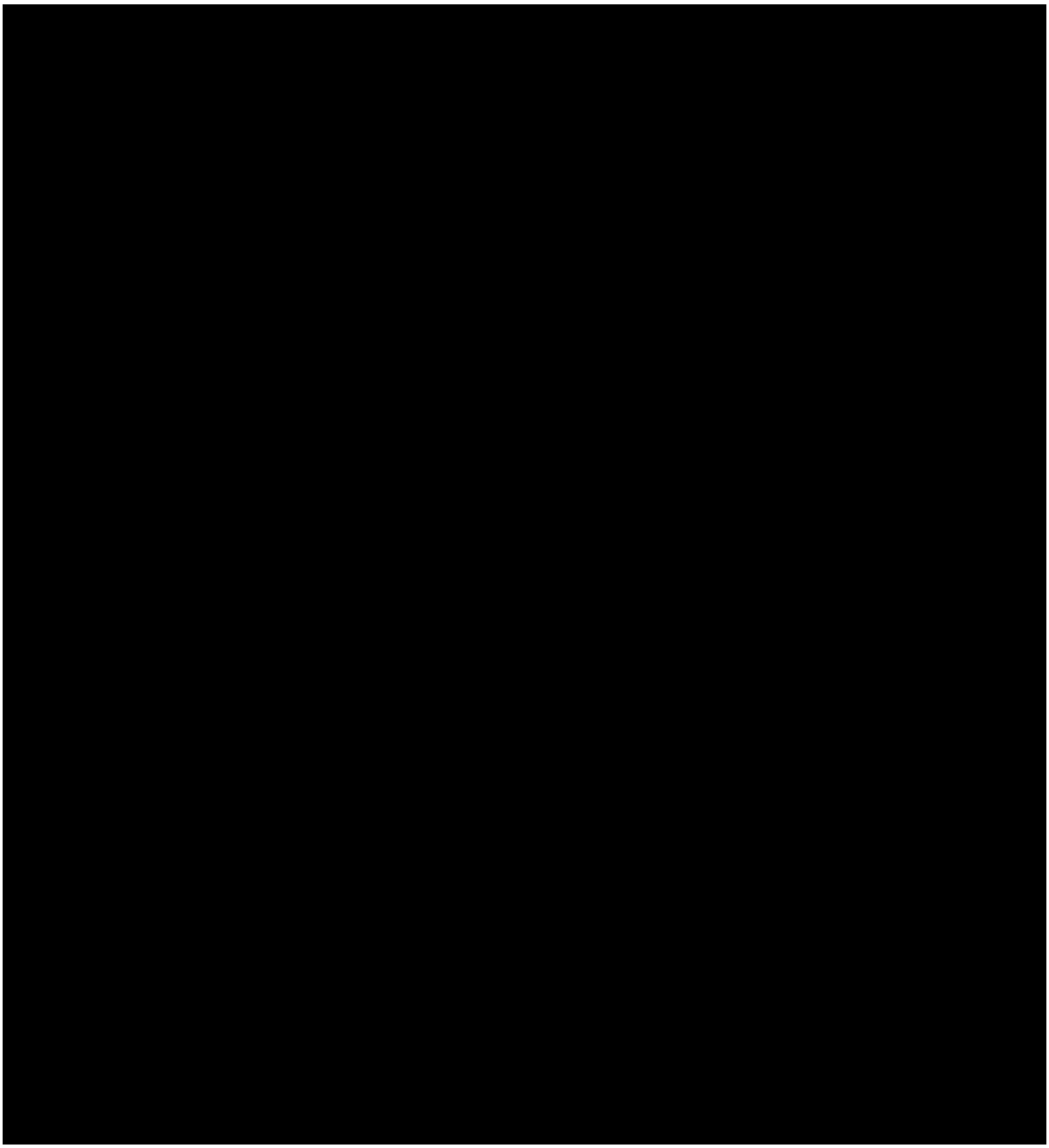
4.1.2. Secondary Endpoints

The secondary endpoints are:

1. Annualized rate of severe respiratory exacerbations, defined as new onset of symptoms or clinical worsening of respiratory symptoms requiring systemic corticosteroid treatment for ≥3 consecutive days; for patients who are on maintenance systemic corticosteroids, at least double the dose of maintenance systemic corticosteroids for ≥3 consecutive days (with or without antibiotic therapy if indicated) over the 24- to 52-week treatment period
2. Annualized rate of ABPA-related exacerbations, defined as severe respiratory exacerbations (as defined above) that are associated with a doubling of serum total IgE from the prior pre-exacerbation value, over the 24- to 52-week treatment period
3. Annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility during the 24- to 52-week treatment period
4. Change from baseline in ACQ-5 over the 24- to 52-week treatment period
5. Change from baseline in SGRQ total score over the 24- to 52-week treatment period
6. Percentage of participants achieving a reduction in the SGRQ score of 4 points or greater from baseline to weeks 12, 24, 36, and 52
7. Percent change from baseline in total IgE in serum over the 24- to 52-week treatment period
8. Percent change from baseline in *A fumigatus*-specific IgE in serum over the 24- to 52-week treatment period
9. Percent and absolute change from baseline in FeNO over the 24- to 52-week treatment period
10. Incidence of treatment-emergent adverse events (TEAEs) from baseline through the end of treatment (week 24 to 52)
11. Immunogenicity of dupilumab, as determined by the incidence, titer, and clinical impact of treatment-emergent ADA to dupilumab over time
12. Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to the end of study

4.1.3. Exploratory Endpoints

The exploratory endpoints are:



5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics, medical/surgical history, medication history, smoking history, spirometry and FEV1 reversibility, hepatitis and human immunodeficiency virus (HIV) serology, serum pregnancy test for women of childbearing potential (WOCBP), blood eosinophil count, total serum IgE, *A fumigatus* skin testing, serum *A fumigatus*-specific IgE, serum *A fumigatus*-specific IgG, *Aspergillus* serum precipitins, and radiological assessment with findings consistent with ABPA.

5.2. Efficacy Variables

The efficacy variables include counts or measurements for individual patients of the following: number of severe respiratory exacerbations over the treatment period, pre- and post-bronchodilator FEV1, [redacted], number of severe respiratory exacerbations over the treatment period that are associated with doubling of serum total IgE from the prior pre-exacerbation value, number of severe respiratory exacerbations that are associated with hospitalization, ED or urgent care visits, assessments of systemic corticosteroid use, [redacted]. Patient-reported outcome measures to assess HRQoL and asthma control include SGRQ total score and ACQ-5 score.

5.3. Safety Variables

The safety variables include vital signs, physical examination, electrocardiograms (ECGs), laboratory evaluations (hematology, chemistry, and urinalysis), urine pregnancy test (females), and adverse events (AEs).

5.4. Pharmacokinetic Variables

Concentrations of functional dupilumab in serum at each time point will be considered to be trough values (C_{trough} time point). These sampling time points are specified in Table 1.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1.

5.6. Pharmacodynamic and Other Biomarker Variables

The pharmacodynamic and biomarker variables are:

- FeNO
- Total IgE in serum
- *A fumigatus*-specific IgE in serum
- [redacted]
- [redacted]

6. STUDY DESIGN

6.1. Study Description and Duration

This phase 2, global, multicenter, randomized, double-blind, placebo-controlled study of dupilumab is designed to evaluate the efficacy and safety of dupilumab in patients with ABPA. Approximately 60 patients will be enrolled in the study. The study consists of 3 study periods:

- Screening period (4 weeks)
- Randomized treatment period (24- to 52 weeks)
- Post-treatment follow-up period (12 weeks)

This study employs a variable treatment duration from 24- to 52 weeks. Patients enrolled in the trial will remain in the treatment period for up to a maximum of 52 weeks or until the last patient completes a minimum treatment period of 24 weeks. Of note, the accrual and drop-out rates will be closely monitored. The maximum treatment duration of 52 weeks will not be changed. For further explanation regarding the duration of the randomized treatment period, refer to Section 9.1.1.

Patients who meet the eligibility criteria will be randomized (1:1) to 1 of the following treatment groups:

- Dupilumab 300 mg, after a loading dose of 600 mg on day 1, administered SC Q2W
- Matching placebo, administered SC Q2W

Randomization will be stratified by region (pooled country), chronic systemic corticosteroid use (yes/no) at screening, and by oral antifungal use (yes/no) at screening.

Rescue courses of systemic steroids for exacerbations, as determined by the investigators, will be permitted during the study. Patients will be required to continue all background asthma controller medications (ICS) with or without long-acting beta agonist (LABA), leukotriene receptor antagonist (LTRA), or long-acting muscarinic receptor antagonist (LAMA) without any changes in the dose or regimen during the study period. However, if 2 or more exacerbations occur during the treatment period, changes to background therapy (eg, changes to background asthma controller medication or initiation of antifungal therapy) may be made at the investigator's discretion.

Patients on Chronic Oral Corticosteroids at Baseline:

Patients who experience a severe respiratory exacerbation will have, as soon as possible, an unscheduled visit at the site for the collection of a blood sample for serum total IgE measurement.

Patients who withdraw from the study prematurely will have, at the time of their next regularly scheduled visit, an early termination visit. This early termination visit will consist of all assessments normally planned for the end of study (EOS) visit. To allow assessment of patient outcomes over the stipulated study period, patients who discontinue study treatment but continue in the study will be asked and encouraged to complete all remaining study visits and participate in all safety follow-up assessments according to the visit schedule (Table 1).

Patients on Oral Antifungals:

For patients receiving oral antifungal therapy during the 24- to 52-week treatment period, the dose and regimen of the oral antifungal agent should remain stable until the end of the treatment period. However, antifungal discontinuation or modification to the dose or regimen is permitted for the following reasons: side effects, intolerance, or lack of efficacy (eg, acute exacerbation) as determined by the investigator. Initiation of therapy with oral antifungal agents is permitted if 2 or more exacerbations occur during the course of the study.

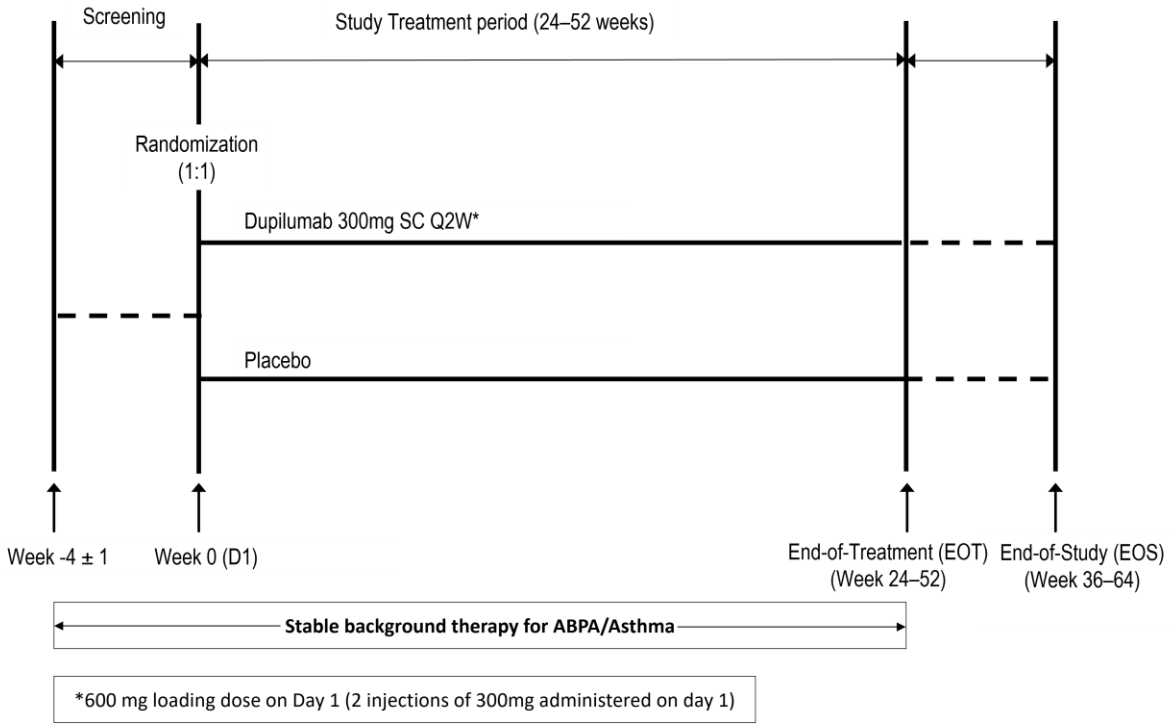
Blood Immunophenotyping Substudy (Optional):

A blood phenotypic substudy may be performed at selected sites. Only patients who are not on chronic systemic steroids and not on antifungal therapy at baseline and provide a separate written informed consent will be eligible to participate in the blood immunophenotyping substudy. A blood sample will be collected at time points outlined in the Schedule of Events Table 1. Blood may be immunophenotyped and sorted using flow cytometry or other methods and characterized using RNA sequencing or other methods to quantitate mRNA.

Post-Treatment Follow-Up Period:

Upon completing the randomized treatment period, patients will continue their background therapy and enter a 12-week safety follow-up period. Adjustment of background asthma and ABPA medications will be allowed at the discretion of the investigator as clinically indicated during the post-treatment follow-up period.

Figure 1: Study Flow Diagram



Note: Upon implementation of amendment 3, the treatment period for all participants will be a minimum of 24 weeks and a maximum of 52 weeks. The week of EOT and EOS will vary accordingly.

NOTE: If there are restrictions to the clinical study as a result of the COVID-19 pandemic, it may be necessary to adjust the visit schedule, convert in-person visits to telephone contacts, and postpone study procedures until the next available study visit. It is necessary that the randomization visit (V2) occur in the clinic. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency. Once local COVID-19 conditions resolve, all study visits and procedures should follow the schedule of events as specified in the Schedule of Events (Table 1).

6.1.1. End of Study Definition

The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

No interim analysis is planned.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC), composed of members who are independent from the sponsor and the investigators, will monitor patient safety by conducting formal periodic reviews of cumulative or periodic safety data that will be blinded by treatment group. The IDMC may request and be provided the unblinded safety data, or any other requested data, for the purposes of a risk/benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also recommend any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 60 patients (approximately 30 patients per arm) will be enrolled globally.

7.2. Study Population

This study will enroll ABPA patients who meet modified ISHAM working group 2013 criteria for ABPA (Agarwal, 2013). These diagnostic criteria for ABPA are widely accepted clinically and broadly divided into 'obligatory' and 'other' supportive criteria (Agarwal, 2013).

The overall goals of treatment of ABPA include reduction of symptoms of ABPA, reducing pulmonary inflammation, and treatment of exacerbations to prevent progression of lung disease. Systemic corticosteroids have been the mainstay of treatment for ABPA, but toxicities limit their use. Approximately 25% to 35% of ABPA patients remain on long-term systemic steroids (corticosteroid-dependent). Patients on chronic systemic corticosteroids with a stable dose of up to 10 mg/day of prednisolone (or its equivalent) or up to 30 mg of prednisolone (or its equivalent) every other day will be allowed to participate in the study to evaluate treatment effects in patients with greater disease severity. Antifungal agents, especially triazoles, are prescribed as an adjuvant therapy in some cases. However, antifungal agents are not curative, their effects on preventing exacerbations are variable, and some of the benefits associated with triazoles may be related to impairment of the metabolism of exogeneous corticosteroids by these agents rather than a direct antifungal effect. Therefore, to minimize confounding effects of these agents, randomization will be stratified by the use of oral antifungal agents (yes/no) at screening.

Rescue courses of systemic steroids for exacerbations, as determined by the investigators, will be permitted during the study. However, to minimize confounding effects of changes in background asthma therapies on the outcome measures, changes to background asthma controller therapy (other than OCS use as described above) will not be permitted unless the patient has had 2 or more severe exacerbations during the treatment period. Once 2 or more severe exacerbations have occurred during the treatment period, changes to background asthma controller therapy may be made at the investigator's discretion.

Patients with post-bronchodilator airflow obstruction ([redacted]) will be permitted to enroll, since mucus plugging and bronchiectasis may limit bronchodilator reversibility. However, patients with severely reduced lung function ([redacted] will not be permitted to participate.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Males and females ≥12 years of age at screening
2. Diagnosis of ABPA defined by the following criteria at screening:

   Obligatory criteria at screening (must meet all 3 of the following criteria):

a. Physician diagnosis of asthma for at least 12 months based on the Global Initiative for Asthma (GINA) 2019 guidelines
b. Evidence of sensitization to *A fumigatus* by skin testing (at screening or documented historical positive skin test in the previous 12 months), or elevated *A fumigatus*-specific IgE in serum (≥0.35 kU/L) at screening
c. Elevated serum total IgE >1000 IU/mL. If all 3 supportive criteria for ABPA (below) are met, IgE ≤1000 IU/mL is acceptable. If the patient is receiving OCS at screening, a documented historical IgE > 1000 IU/mL within the previous 12 months is acceptable

And 2 or more of the following supportive criteria:

a. For patients on OCS, blood eosinophil count >500 cells/µL at screening or a documented historical blood eosinophil count >500 cells/µL within 12 months of screening. For patients not on OCS, blood eosinophil count >500 cells/µL at screening or blood eosinophil ≥300 to ≤500 cells/µL at screening with a documented historical blood eosinophil count >500 cells/µL within 12 months of screening.
b. The presence of serum precipitating or IgG antibodies to *A fumigatus* at screening or a documented historical positive result for one of these tests within 12 months prior to screening
c. Documented radiological findings consistent with ABPA (such as fleeting pulmonary parenchymal opacities, mucoid impaction, high-attenuation mucus, centrilobular nodular opacities, atelectasis, bronchiectasis, etc) by historical chest x-ray or chest computed tomography (CT) or magnetic resonance imaging (MRI) within the previous 18 months or at screening

NOTE: A total of 2 attempts may be made during the screening period until the baseline visit to meet the qualifying criteria for blood eosinophils, total serum IgE, Aspergillus-specific IgE, Aspergillus-specific IgG, Aspergillus precipitins, and/or skin prick test

3. On a maintenance therapy for their asthma with controller medication which must include ICS and may include 1 or more additional controller medications including a LABA, LTRA, and/or LAMA, etc for at least 12 weeks, with a stable dose and regimen with no change in the dose or frequency of administration for at least 4 weeks prior to the screening visit, and between the screening and baseline/randomization visits
4. For patients on OCS: must be on a chronic stable dose (no change in the dose) of OCS of up to 10 mg/day (for patients taking daily corticosteroids) or up to 30 mg every alternate day (for patients taking alternate day corticosteroids) (prednisone/prednisolone or the equivalent) for at least 4 weeks prior to the screening visit and between the screening and the baseline/randomization visit. In addition, patients must agree to switch to study-required prednisone/prednisolone as their OCS at visit 1 and use it per protocol for the duration of the study.
5. Must have experienced ≥1 severe respiratory exacerbation requiring treatment with systemic corticosteroids or hospitalization or treatment in ED/urgent care within 12 months prior to the screening visit, or must be receiving chronic stable low-dose OCS (see inclusion criterion #4)
6. ACQ-5 score of ≥1.5 at screening and at baseline visit

7. For those participating in the blood immunophenotyping substudy, must not have received systemic corticosteroids or oral antifungals from 4 weeks prior to screening through randomization
8. Willing and able to comply with clinic visits and study-related procedures
9. Able to provide signed informed consent/assent (by study patient or legally acceptable representative). For adolescents, parent or legal guardian must provide signed informed consent (patients must also provide separate informed assent to enroll in the study, and the assent documented either in a separate informed assent form or in the informed consent form [ICF] signed by the parent(s)/legal guardian(s) [as appropriate based on local regulations and requirements])
10. For patients receiving oral antifungals at baseline: must be on a stable dose and regimen of antifungal agent for at least 4 weeks prior to screening and between the screening and baseline visit.

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Weight less than 30.0 kilograms
2. Current smoker or e-cigarette user, cessation of smoking or e-cigarette use within 6 months prior to randomization, or ≥10 pack-years smoking history
3. Post-bronchodilator FEV1 <30% predicted normal at screening
4. (Exclusion criterion #4 was removed in Protocol Amendment 2)
5. For those receiving OCS at baseline: considered to be at high risk for adverse events due to tapering of OCS, in the opinion of the investigator
6. Respiratory exacerbation requiring systemic corticosteroids within 4 weeks prior to screening and between screening and baseline visit (for patients on daily or alternate day OCS, exacerbation requiring at least double the maintenance dose of corticosteroids)
7. Upper or lower respiratory tract infection within the 4 weeks prior to screening (visit 1) or between the screening and randomization visits
8. Significant chronic pulmonary disease other than asthma complicated with ABPA (eg, physician-diagnosed bronchiectasis due to a condition other than ABPA; cystic fibrosis; sarcoidosis; interstitial lung disease not due to ABPA; chronic obstructive pulmonary disease [COPD] not due to ABPA; hypereosinophilic syndrome; etc), a diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts
9. Diagnosis or suspected diagnosis of EGPA (also called Churg-Strauss Syndrome)
10. Diagnosis of aspergilloma, invasive or disseminated aspergillosis, or chronic pulmonary aspergillosis
11. Severe cor pulmonale with evidence of right cardiac failure
12. Treatment with supplemental oxygen for >8 hours/day
13. Hypercapnia requiring non-invasive ventilation (eg, bilevel positive pressure ventilation)

14. Patients with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory (other than asthma and ABPA), gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgment of the investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, severe uncontrolled hypertension, severe ischemic heart disease, unstable angina in the last 6 months, uncontrolled Class III or IV cardiac failure according to the New York Heart Association classification, unstable cardiac arrhythmias, hepatobiliary conditions (e.g., Child-Pugh class B or C), demyelinating diseases, active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc)
15. Acute myocardial infarction <6 months from screening visit
16. Hospitalization for any cardiovascular or cerebrovascular event <6 months from the screening visit
17. Known or suspected history of immunosuppression or immunodeficiency disorder including a history of invasive opportunistic infections (eg histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis), despite infection resolution; or unusually frequent, recurrent, or prolonged infections, suggesting an immune-compromised status, as judged by the investigator
18. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) or patients with high titer autoantibodies at screening who are considered by the investigator or the sponsor of having high risk for developing autoimmune disease
19. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix or completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
20. Previous use of dupilumab
21. Initiation, discontinuation, or change in the dosage regimen of SC immunotherapy (SCIT) within 3 months prior to visit 1
    a. Patients on a stable dose of these medications for at least 1 year prior to visit 1 may be included in the study, but must not change the dose during the study
22. Treatment with sublingual immunotherapy (SLIT)
23. Patients who have received or initiated bronchial thermoplasty within 3 years prior to visit 1 or plan to begin therapy during the screening period or the randomized treatment period

24. Anti-IgE therapy (eg omalizumab [Xolair®]) within 130 days prior to visit 1 or any other biologic therapy (including anti-IL5, anti-IL5R, anti-IL4rα, anti-IL13 monoclonal antibodies) or systemic immunosuppressant (eg methotrexate, any anti-TNF drugs, Janus kinase inhibitors, B and/or T cell-targeted immunosuppressive therapies) to treat inflammatory disease or autoimmune disease (eg rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) and other diseases, within 3 months or 5 half-lives prior to screening, whichever is longer
25. Exposure to another investigational drug (monoclonal antibodies as well as small molecules) within a period prior to screening, as follows: an interval of less than 6 months or at least 5 half-lives for investigational monoclonal antibodies, and an interval of less than 30 days for investigational small molecules
26. History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients, or a contraindication to treatment with dupilumab per the approved local prescribing information
27. Treatment with a live (attenuated) vaccine within 4 weeks prior to the baseline visit or planned live attenuated vaccinations during the study
28. Patients with active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis, or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent in the medical judgment of the investigator and/or infectious disease specialist. (Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees [ECs].)
29. Diagnosed active parasitic infection (helminths), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization
30. HIV by clinical or serological history
31. Established diagnosis of hepatitis B viral infection at the time of screening or positive for hepatitis B surface antigen (HBsAg) at the time of screening:
    a. Patients who have gained immunity for hepatitis B virus infection after vaccination (patients who are HBsAg-negative, hepatitis B surface antibody [HBsAb]-positive, and hepatitis B core antibody [HBcAb]-negative are eligible for the study)
    b. Patients with positive HBcAb are eligible for the study only if hepatitis B virus DNA level is undetectable.
32. Established diagnosis of hepatitis C viral (HCV) infection at the time of screening. Patients positive for hepatitis C Ab are eligible for the study only if HCV RNA is negative
33. Liver injury-related criteria:
    a. Clinically significant/active hepatobiliary disease or evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] more than 3 times the upper limit of normal [ULN] during the screening period)

34. Any of the following abnormal lab values at screening:
    a. Creatine phosphokinase (CPK) >10 ULN or
    b. Platelets <100,000 cells/mm^3

    NOTE: If an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality would the patient be categorized as a screen failure.
35. Known or suspected alcohol and/or drug abuse within 2 years before the screening visit, or evidence of such abuse as documented by a positive result in a laboratory test for alcohol and/or drug panel conducted at the screening visit

    NOTE: If a patient has a positive drug test for a prescription drug being used for medical reasons, the patient would still be eligible for enrollment. In such cases, the site would need to confirm the medical reason for use with the treating physician.
36. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents
37. Inability to follow instructions or complete study-related procedures (eg due to language problems or psychological disorders)
38. Individuals accommodated in an institution by virtue of an order issued either by the judicial or the administrative authorities; prisoners or patients who are legally institutionalized
39. Patient or his/her immediate family is a member of the dupilumab investigational team
40. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
41. WOCBP* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner (provided that the partner is the sole sexual partner of the WOCBP patient and that the vasectomized partner has received medical assessment of the surgical success for the procedure)
    e. and/or sexual abstinence†, ‡

*Women of childbearing potential are defined as women who are fertile, following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance.

Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

42. Any country-specific regulation that would prevent the participant from entering the study

NOTE: Patients who do not meet the inclusion criteria or fail the exclusion criteria (eg due to a transient reason) may be rescreened once, after consultation with the medical monitor. Rescreened patients will be assigned a new patient ID versus the one received for the initial screening. There is no requirement for a waiting period between the screen-failure date and the rescreening.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.4.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study/study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Dupilumab drug product is supplied for this study in the following concentration:

- Dupilumab 150 mg/mL: Each 2.0 mL single-use prefilled glass syringe with snap-off cap delivers 300 mg of study drug (2.0 mL of a 150 mg/mL solution)
- Placebo-matching dupilumab is prepared in the same formulation without the addition of protein (ie active substance, anti-IL-4Rα monoclonal Ab).

Study drug will be administered by SC injections. Subcutaneous injection sites of study drug should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations.

Dupilumab will be administered as a 600 mg loading dose on day 1, followed by 300 mg administered SC Q2W.

Matching placebo will be administered SC Q2W.

Instructions on dose preparation are provided in the pharmacy manual.

8.2. Background Treatments

Prior to screening, patients must be on a stable background therapy for asthma for at least 3 months with a stable dose ≥1 month, and all background therapy must remain stable between screening and baseline. Asthma controller medications must include ICS and may include 1 or more additional controller medications (eg, LABA, LTRA, LAMA). Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to screening and between screening and baseline.

Patients requiring systemic corticosteroids (prednisone or equivalent) up to 10 mg per day, or up to 30 mg every other day, for ABPA are also permitted. Oral corticosteroid doses will be down-titrated starting 4 weeks after randomization according to the schedule described in Appendix A.

Patients receiving oral antifungal therapy at baseline are permitted to enroll. For patients receiving antifungal therapy during the 24- to 52-week treatment period, the dose and regimen should remain stable until the end of the treatment period. However, antifungal discontinuation or modification to the dose or regimen is permitted for the following reasons: side effects, intolerance, or lack of efficacy (eg, acute exacerbation) as determined by the investigator.

Patients will be required to continue all background asthma controller medications (ICS) with or without long-acting beta agonist (LABA), leukotriene receptor antagonist (LTRA), or long-acting muscarinic receptor antagonist (LAMA) without any changes in the dose or regimen during the study period. However, if 2 or more exacerbations occur during the treatment period, changes to background therapy (eg, changes to background asthma controller medication or initiation of antifungal therapy) may be made at the investigator's discretion.

8.3. Rescue Treatments

Short-acting bronchodilators (SABA) are permitted as rescue therapy throughout the study. Rescue therapy with ICS and/or LABAs is not permitted.

Systemic corticosteroids are allowed as rescue treatment for exacerbation. The need for rescue therapy and dosage will be determined by the site investigator. For patients on chronic systemic corticosteroids, an increase in the dose of systemic steroids is allowed as rescue treatment.

If 2 or more exacerbations occur during the treatment period, antifungal therapy may be initiated (or the dose may be increased for patients on antifungal therapy) after consultation with the medical monitor at the discretion of the investigator.

Patients receiving rescue therapy permitted by the protocol may continue to receive study drug. They will remain blinded and will be asked to return to the clinic for all remaining study visits for the double-blind treatment period and the follow-up period, and participate in all assessments for these visits according to the Schedule of Events specified in Table 1.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Study drug dose modification for an individual patient is not allowed.

8.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction (eg, Hy's law is met ([Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation FDA 2009])
- Patient withdraws consent
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- In the event of a critical protocol deviation, at the discretion of the investigator or the sponsor
- At the specific request of the sponsor

- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin. Patient must be withdrawn for these latter malignancies if they cannot be adequately treated by local resection.
- Any opportunistic infection or other infection whose nature or course may suggest an immunocompromised status
- Severe laboratory abnormalities assessed as related to study drug:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values >3 × ULN with total bilirubin >2 × ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of study drug for the concerned patient. See Table 1 for information on follow-up and any further evaluations that need to be completed.

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily discontinued in the event of:

- Severe laboratory abnormalities (as noted in Section 8.4.2.1) where a causal relationship to study drug can be reasonably excluded, (ie, an alternative cause is evident): study drug will be discontinued but may be resumed when the laboratory abnormality is sufficiently normalized. At minimum, the laboratory value(s) must return to a level that no longer meets the specified criteria for discontinuation, as defined in Section 8.4.2.1. A decision to resume study treatment will be made jointly by the investigator and medical monitor.
- Infections or infestations that do not respond to medical treatment
- Other intercurrent illness or adverse event or major surgery which could, in the opinion of the investigator, present an unreasonable risk to the patient as a result of his/her continued use of the study drug

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron Pharmaceuticals, Inc. medical monitor. Re-initiation of treatment with the study drug will be done under close and appropriate clinical and/or laboratory monitoring once the investigator will have considered, according to his/her best medical judgment, that the AE is sufficiently resolved and unlikely to recur after resuming therapy with the study drug.

The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the Regeneron medical

monitor should be contacted as soon as possible. Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical monitor.

For visits other than the randomization and EOT visits, if a patient is unable to return to the clinic for a given visit within the specified visit window, any follow-up procedures scheduled for the missed visit should be performed at the subsequent visit.

If the patient misses more than 4 consecutive doses, the patient will be permanently discontinued from the study.

For all temporary discontinuations of study intervention, duration must be recorded by the investigator in the electronic case report form (eCRF). Following a temporary interruption or missed dose, the investigational medicinal product (IMP) treatment should be reinitiated at the next scheduled visit, maintaining the original dose.

If a patient requires a prohibited medication at any time during the study, the investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.5. Management of Acute Reactions

8.5.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following SC injection of study drug should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.6. Method of Treatment Assignment

Approximately 60 patients will be randomized at baseline/week 0/visit 2 in a 1:1 ratio to receive either dupilumab 300 mg Q2W or placebo 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 will be stratified by region (pooled country), by chronic systemic corticosteroid use (yes/no) at screening, and by oral antifungal use (yes/no) at screening.

8.7. Blinding

Study patients, the principal investigators, and study site personnel will 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 will remain blinded to all patient randomization assignments.

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

Anti-drug antibody, drug concentration results, and post-treatment biomarker results ([redacted], serum total IgE, and *A fumigatus*-specific IgEs) will not be communicated to the sites, and

the sponsor's operational team will not have access to results associated with patient identification until after the database is locked for the respective study part.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded/unmasked (Section 8.4.2).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind/unmask the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.10. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.10.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited during the study:

- Systemic immunosuppressive/immunomodulating drugs (including, but not limited to: omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, or other biologics) other than protocol-defined use of corticosteroids
- Treatment with an investigational drug (other than dupilumab)
- Initiation of SCIT, or change in dose for those patients on a stable dose of SCIT within 1 year prior to screening
- SLIT
- Oral immunotherapy
- Treatment with a live (attenuated) vaccine:
  - Chickenpox (varicella)
  - FluMist-influenza
  - Intranasal influenza
  - Measles (rubeola)
  - Measles-mumps-rubella combination
  - Measles-mumps-rubella-varicella combination

  - Mumps
  - Oral polio (Sabin)
  - Oral typhoid
  - Rubella
  - Smallpox (vaccinia)
  - Yellow fever
  - Bacille Calmette-Guerin
  - Rotavirus
  - Varicella zoster (shingles)
- The following concomitant procedures are prohibited during the study period:
  - Major elective surgical procedures
  - Bronchial thermoplasty

8.10.2. Permitted Medications

Other than the prohibited medications listed in Section 8.10.1, treatment with concomitant medications are permitted during the study. This includes topical and systemic anti-infective medications for any duration, use of contraceptives, nasal and inhaled corticosteroids, and oral antihistamines for any duration. Antifungal therapy to treat ABPA is described in Section 8.2.

Medications used to treat chronic diseases such as diabetes, hypertension, and asthma (ICS plus 1 or more additional controller medications [eg, LABA, LTRA, LAMA, etc], and/or systemic steroids [see Section 8.2]) are permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

		Randomized treatment period**																														
Study Procedure	Screening Visit[a]	Randomization/ Baseline Visit[b]																												EOT visit	EOS visit	Unscheduled Visit[z]
												Phone call visits				Phone call visits						Phone call visits				Phone call visits						
Week	-4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	24-52**	36-64	
Visit	1	2[c]	3	4	5*	6	7*	8	9*	10*	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	14-28	15-29	
Window (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	
Screening/Baseline:																														
Inclusion/ Exclusion	X	X																												
Informed Consent/Assent	X																													
Medical and surgical history	X																													
Demographics	X																													
Pre- and post-bronchodilator spirometry[d,e]	X																													
Qualifying ACQ-5	X																													
ANCA, Hepatitis and HIV serology[f]	X																													
Tuberculosis testing[g]	X																													
Serum pregnancy test[h,i]	X																													
A fumigatus skin testing	X																													
Serum IgG and precipitins against *A fumigatus*	X																													

		Randomized treatment period**																														
Study Procedure	Screening Visit[a]	Randomization/ Baseline Visit[b]																												**EOT visit**	**EOS visit**	**Unscheduled Visit[r]**
											Phone call visits												Phone call visits				Phone call visits						
Week	-4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	24-52**	36-64	
Visit	1	2[c]	3	4	5*	6	7*	8	9*	10*	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	14-28	15-29	
Window (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	
[redacted]																														
Urine toxicology	X																													
Smoking history	X																													
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																												
Treatment:																														
Call IVRS/IWRS[k]	X	X	X	X	X*	X	X*	X	X*	X*				X						X				X				X	X	
Administer study drug[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense /Review home dosing paper diary	X	X	X	X	X*	X	X*	X	X*	X*				X						X				X				X		X
OCS dose titration for pts on OCS at baseline				X	X*	X	X*	X	X*	X*																				
Efficacy:																														
Spirometry[d]		X	X	X	X*	X	X*	X	X*	X*				X						X				X				X	X	
Post-BD spirometry[d]		X	X	X				X						X						X								X		
ACQ-5 score[m]		X	X	X	X*	X	X*	X	X*	X*				X						X				X				X	X	
SGRQ Score[m]		X		X				X						X						X								X	X	

		Randomized treatment period**																														
Study Procedure	Screening Visit[a]	Randomization/ Baseline Visit[b]																												**EOT visit**	**EOS visit**	**Unscheduled Visit[r]**
											Phone call visits				Phone call visits							Phone call visits				Phone call visits						
Week	-4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	24-52**	36-64	
Visit	1	2[c]	3	4	5*	6	7*	8	9*	10*	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	14-28	15-29	
Window (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	
Safety:																														
Vital Signs[n]	X	X	X	X	X*	X	X*	X	X*	X*				X						X				X				X	X	X
Physical examination[o]	X	X		X				X						X						X								X	X	X
Electro-cardiogram[p]	X																											X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:																														
Hematology[q]	X	X		X		X		X						X						X				X				X	X	X
Blood chemistry[r]	X	X		X				X						X						X								X	X	
Urinalysis[s]	X	X												X														X	X	
Urine pregnancy test[t]		X		X		X		X						X						X				X				X	X	
Pharmacokinetics and ADA Sampling																														
Drug concentration sample[u]		X						X						X														X	X	
ADA sample[u]		X						X						X														X	X	
Biomarkers:																														
FeNO[v]	X	X		X		X		X						X						X				X				X	X	
Serum total IgE[w]	X[e]	X		X		X		X						X						X								X	X	X
Serum *A fumigatus* specific IgE	X[e]	X		X				X						X						X								X	X	

		Randomized treatment period**																														
Study Procedure	Screening Visit[a]	Randomization/ Baseline Visit[b]																													**EOT visit**	**EOS visit**	**Unscheduled Visit[z]**
												Phone call visits				Phone call visits						Phone call visits				Phone call visits						
Week	-4	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	24-52**	36-64	
Visit	1	2[c]	3	4	5*	6	7*	8	9*	10*	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	14-28	15-29	
Window (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	
Pharmacogenomics and future biomedical research:																														
Blood samples for future Biomedical research		X		X				X						X						X				X				X		
Whole blood RNA[x] (optional)		X																												
Whole blood for DNA[x] (optional)		X																												
Blood immunophenotyping substudy[y] (optional)		X		X				X																				X		

NOTE: EOS is end of study; the follow-up period begins at the EOT visit and ends at the EOS visit.

9.1.1. Footnotes for the Schedule of Events Table

Footnotes for Table 1 Schedule of Events

*Visits 5, 7, 9, and 10 will be performed as phone visits for patients not receiving OCS at baseline. For patients receiving OCS at baseline, these visits should be performed in-clinic if the patient remains on OCS on the day of the clinic visit. If OCS has been discontinued, these visits can be either in-clinic or performed as a phone visit at the discretion of the investigator. Assessments/procedures marked with an asterisk should only be performed if the visit occurs in-clinic.

**After the last patient has completed visit 14/week 24 of the treatment period or withdrawn from the study, all patients still currently in the treatment period (between visit 15/week 26 and visit 27/week 50) should return to the clinic 2 weeks from their last dose/treatment administration to complete their EOT visit and all its applicable assessments. For patients who have withdrawn from the study treatment but remain in the study, the EOT visit will take place 2 weeks from their last visit. All patients must have their EOS visit 12 weeks after their EOT visit.

a. Prior to screening, patients must be on a stable background therapy for asthma which may include ICS in combination with a second controller medication (eg, LABA, LTRA, theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to baseline. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to visit 1. Patients requiring systemic steroids of up to 10 mg per day (or up to 30 mg every alternate day) as controller medication are permitted.
b. Randomization/baseline visit is defined as day 1. The visit schedule should be adhered to within ±1 week for the screening period, ±3 days for the randomized IMP treatment period, and ±7 days for the post-IMP treatment period.
c. All assessments at visit 2 (day 1) are to be conducted pre-IMP dose except for the assessment of local tolerability of SC injections.
d. Spirometry will be done locally according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidance, but measured by a central laboratory. Spirometry will be performed during a trough period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of ipratropium for at least 8 hours, withholding the last dose of LABA for at least 12 hours (ultra-long-acting LABA-like vilanterol should be withheld for at least 24 hours), and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements. Post-bronchodilator FEV1 will be determined at the designated treatment visits.
e. Three attempts may be made during the screening period until the baseline visit to meet the qualifying criteria for FEV1. A total of 2 attempts may be made during the screening period until the baseline visit to meet the qualifying criteria for blood eosinophils, total serum IgE, *Aspergillus*-specific IgE, *Aspergillus*-specific IgG, *Aspergillus* precipitins, and/or skin prick test.

f. Clinical laboratory testing at screening visit 1 will include hepatitis screen covering HBsAg, HBsAb, HBcAb), hepatitis C virus antibodies, HIV screen (anti-HIV-1 and anti-HIV-2 antibodies). In case of results showing HBsAg (negative), and HBcAb (positive), an HBV DNA testing will be performed prior to randomization to rule out a false positivity if the investigator believes the result is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.

g. Patients with active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis, or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated, and can now start treatment with a biologic agent in the medical judgment of the investigator and/or infectious disease specialist. (Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees [ECs].)

h. Only for women of childbearing potential. Pregnancy will lead to definitive treatment discontinuation in all cases. In case of positive urinary test, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy.

i. Serum pregnancy test will be conducted at visit 1 and urine dipstick pregnancy tests will be conducted at other visits. A negative result must be obtained at visits 1 and 2 prior to randomization.

j. [redacted]

k. IVRS/IWRS will be utilized during screening to assign screening IDs, during baseline to provide treatment assignments to the investigator, and to dispense study drug.

l. Every 2 weeks, study drug administrations must be separated by at least 11 days. IMP can be administered in clinic at scheduled visits or at home (patient, caregiver, or health care professional). Patients and parents/caregivers who prefer to have clinic staff administer study drug may choose to have injections administered in the clinic. Due to the COVID-19 pandemic, study drug may be shipped from the clinical site to the patient's home if necessary.

m. ACQ-5 and SGRQ are completed in the electronic diary during clinic visits and prior to spirometry at each visit. NOTE: If COVID-19 restrictions limit the availability of staff or the patient to have in-clinic visits, site staff should make every effort to conduct telephone interviews to complete these questionnaires. Site staff should conduct the telephone interviews on the date of scheduled site visit by following an interview guide provided by the sponsor. Patient responses from the interviewer administered questionnaires will be captured by the site staff.

n. Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and respiratory rate will be measured at screening, baseline, and every subsequent on-site visit. For adults, height (cm) will be measured only

at screening (visit 1), and body weight (kg) will be measured at screening (visit 1) and at EOT/EOS visits. For adolescents, height and body weight will be measured at the screening and randomization visits (visits 1 and 2) and every subsequent visit.

o. Complete physical examinations will include skin, nasal cavities, eyes, ears, and respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

p. 12-lead ECG is to be read centrally.

q. Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count, differential count, and total red blood cell (RBC) count.

r. Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count.

s. Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen, and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.

t. Serum pregnancy test will be conducted at visit 1 and urine dipstick pregnancy tests will be conducted at other visits. A negative result must be obtained at visits 1 and 2 prior to randomization.

u. Pharmacokinetic (PK) and ADA samples are to be collected prior to the administration of the drug. In the event of suspected serious adverse events (SAEs), such as anaphylaxis or hypersensitivity, additional samples for the analysis of ADA and dupilumab drug concentration may be collected as close to the event as practically possible.

v. Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

w. If the patient experiences an exacerbation, an unscheduled visit is to be performed for the collection of an additional blood sample for serum total IgE at the time of, or as soon as possible after, the exacerbation.

x. If collection is not completed at randomization, sample can be taken at a following visit. To be collected prior to IMP administration

y. Blood samples will be collected at selected sites. Only patients who are not on chronic systemic corticosteroids and not on oral antifungal therapy at baseline will be allowed to participate in the blood immunophenotyping substudy.

z. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason as warranted. If the patient develops a respiratory exacerbation, he/she will be required to have an unscheduled visit as soon as possible, and a blood sample for serum total IgE needs to be collected.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic once at the time of the next regularly scheduled visit for an early termination visit consisting of the end of study assessments described in Table 1.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, during respiratory exacerbation, or for any other reason as warranted.

9.1.4. End of Treatment Visit

After the last patient has completed visit 14/week 24 of the treatment period or withdrawn from the study, all patients still currently in the treatment period (between visit 15/week 26 and visit 27/week 50) should return to the clinic 2 weeks from their last dose/treatment administration to complete an EOT visit consisting of the assessments described in Table 1. For patients who have withdrawn from the study drug but remain in the study, the EOT visit will take place 2 weeks from their last visit.

9.2. Study Procedures

9.2.1. Procedures Performed at the Screening/Baseline Visit

The following procedures will be performed for the purpose of determining study eligibility or characterizing the baseline population: informed consent/assent, medical and surgical history, demographics, smoking history, qualifying ACQ-5, pre- and post-bronchodilator spirometry, hepatitis and HIV serology, serum IgG against *A fumigatus*, serum precipitins to *A fumigatus*, *A fumigatus* skin testing, serum pregnancy testing, urine toxicology for drug screening, randomization, and tuberculosis testing as guided by country local authorities.

Eligible patients must meet all of the inclusion criteria and none of the exclusion criteria to participate in the study.

9.2.2. Efficacy Procedures

9.2.2.1. Severity of Respiratory Exacerbations

The number of severe respiratory exacerbations will be recorded by the investigator and defined as new onset symptoms or clinical worsening that requires systemic corticosteroid treatment for ≥3 consecutive days, and, for patients who are on maintenance systemic corticosteroids, at least double the dose of maintenance systemic corticosteroids for ≥3 consecutive days plus antibiotic therapy if indicated.

Clinical signs and symptoms of respiratory exacerbation will be captured in the eCRF, including, but not limited to, new onset or increase in cough, wheezing, chest tightness, shortness of breath, sputum volume, and/or change in sputum appearance, etc.

Two events will be considered different if the interval between their start dates is ≥ 28 days.

The reasons (eg, infections including viral and bacterial, allergen exposure, exercise, and others) for the exacerbation events will be collected in eCRF.

9.2.2.2. Lung Function

The following lung function parameters will be measured using spirometry at the clinical site:

- FEV1 (pre- and post-bronchodilator)
- percent predicted FEV1, [redacted]

Spirometry should be performed prior to administration of study drug and in accordance with ATS/ERS guidelines (Miller, 2005).

For pre-bronchodilator measured parameters, including FEV1, [redacted] spirometry will be performed after a washout period of bronchodilators according to their action duration. Examples of washout periods include withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-long-acting LABA, such as vilanterol, should be withheld for at least 24 hours), withholding the last dose of ipratropium for at least 8 hours, and withholding the last dose of LAMA for at least 24 hours. Withholding times will be verified before performing the measurements. Note that when both pre- and post-bronchodilator spirometry are assessed, the post-bronchodilator spirometry should be performed 30 minutes after administration of 2 to 4 puffs of albuterol or another SABA.

At all visits, spirometry should be performed in the morning if possible, but if the test can only be done at a different time of the day, the testing should be done at approximately the same time of the day at each visit throughout the study.

A spirometer that meets the ATS/ERS recommendations will be used. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements. Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible.

The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a patient fails to provide repeatable and/or acceptable maneuvers, an explanation should be documented. [redacted]

Further details on spirometry will be available in a separate operational manual provided to the sites.

9.2.2.3. Allergic Bronchopulmonary Aspergillosis-Related Exacerbations

Allergic bronchopulmonary aspergillosis-related exacerbations will be recorded by the investigator and are defined as a severe respiratory exacerbation (as defined in Section 9.2.2.1) associated with a doubling of serum total IgE value compared to the closest value before the onset of the exacerbation. For all respiratory exacerbations, patients will be required to have, as soon as possible, an unscheduled visit at the site for the collection of a blood sample for serum total IgE measurement.

9.2.2.4. Patient-Reported Outcome Questionnaires

Health-related quality of life and disease control will be recorded by patients using patient-reported outcome questionnaires. The questionnaires will be completed in an electronic diary during clinic visits, prior to spirometry.

St. George's Respiratory Questionnaire (SGRQ)

This questionnaire will be completed by the patient at the time points specified in Table 1 The SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation (Nelsen, 2017a).

A total score ranges from 0 to 100. Scores by dimension are calculated for three domains: Symptoms, Activity, and Impacts (Psychosocial). Lower score indicates better QoL.

The first part (Symptoms) evaluates symptomatology, including frequency and severity of cough, sputum production, wheeze, breathlessness, and the duration and frequency of attacks of breathlessness or wheeze.

The second part has 2 components: Activity and Impacts. The Activity section addresses disturbances to patients' daily physical activities. The Impacts section covers a range of effects that chest troubles may have on patients' daily life and psychosocial functions (eg, daily life activities and functioning, employment, physical functioning, emotional impact, stigmatization, and patients' perceptions when treated). The recall period of the questionnaire is over the past 4 weeks.

Psychometric testing has demonstrated its repeatability, reliability, and validity. Sensitivity has been demonstrated in clinical trials (Nelsen, 2017b). A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. The SGRQ has been used in a range of disease groups including asthma, COPD, and bronchiectasis.

Asthma Control Questionnaire (ACQ-5)

The ACQ-5 questionnaire will be completed by the patient at the time points specified in Table 1. The ACQ was designed to measure both the adequacy of asthma control and change in asthma control, which occurs either spontaneously or as a result of treatment.

The ACQ-5 is a short version of ACQ-7. The ACQ-5 score is the mean of the first 5 questions, between 0 (totally controlled) and 6 (severely uncontrolled). A higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. The optimal cut-point score of 1.50 should be used to be confident that a patient has inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the minimal clinically important difference defined by the developer.

Systemic Corticosteroid Use for Patients on Chronic Corticosteroids at Baseline

Systemic corticosteroid use (including reduction or elimination) during the study will be recorded for patients on chronic OCS at baseline.

[redacted]

If a patient experiences a severe exacerbation during the OCS dose reduction, the exacerbation should be treated with the use of oral or parenteral steroids at least double the dose of the current OCS maintenance dose. Following exacerbation treatment, the patient should be placed on the OCS dose 1 step higher than the dose they were on when the exacerbation occurred.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate, height, and weight will be measured at time points according to Table 1.

9.2.3.2. Physical Examination

A thorough and complete physical, including skin, nasal cavities, eyes, ears, respiratory, and cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems examination will be performed at time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 1. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.3.4. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 1. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Additional laboratory tests to be performed include:

- Antineutrophil cytoplasmic antibodies (ANCA) at screening
- Hepatitis screen including HBsAg, HbsAb, HbcAb, HCVAb
- HIV (Anti-HIV-1 and anti-HIV-2 antibodies) serology
- Serum IgG against *A fumigatus*
- *A fumigatus* skin testing
- Serum *A fumigatus*-specific IgE
- Urine toxicology for drug screening
- Pregnancy test: For WOCBP, pregnancy testing will include a serum pregnancy test at screening and urine pregnancy tests at subsequent time points as specified in Table 1.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical/study director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Samples for dupilumab trough concentration measurements will be collected at visits listed in Table 1.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA and NAb assessment will be collected at time points listed in Table 1. Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore how dupilumab may modify the mechanism of action underlying the disease process in ABPA patients. In particular, the role of the IL-4Rα pathway and the effect of dupilumab on FeNO, [redacted], and total and specific IgE in serum will be explored.

Biomarker samples will be collected at time points according to Table 1. Pharmacodynamic marker/biomarker measurements will be performed to determine effects on biomarkers of ABPA or relevant physiological and pathogenic processes. The biomarkers studied are believed to be relevant to the pathophysiology of ABPA, target engagement, mechanism of action of dupilumab, and possible toxicities.

Several biomarkers related to type 2 inflammation will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response: concentrations of FeNO (a marker of airway inflammation), serum total IgE (a product of immunoglobulin class switching driven by IL-4), serum *A fumigatus*-specific IgE, [redacted]

Data analyses will be described in the statistical analysis plan (SAP) and the results will be described in the clinical study report (CSR).

9.2.6.1. Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide is a measure of lung inflammation. FeNO will be performed according to the timepoints in Table 1. FeNO will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion. This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. Further details on the procedure for measuring fractional exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.2.6.2. Serum Total IgE

Patients with ABPA have elevated IgE, and levels are clinically monitored to assess disease activity. Changes in total IgE reflect not only on ABPA but atopy in general. Baseline IgE levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for PD effects of study treatment on total IgE.

Total IgE will be collected according to the time points in Table 1 and measured in serum with a quantitative method (eg, Phadia ImmunoCAP) approved for diagnostic testing.

Detailed instructions for blood sample collection are provided in the study reference manual/site binder or file.

9.2.6.3. Serum *A Fumigatus*-Specific IgE

A fumigatus-specific IgE will be measured in serum from samples collected according to the time points in Table 1 and measured in serum using a method (eg, Phadia ImmunoCAP) approved for diagnostic testing.

Detailed instructions for blood sample collection are provided in the study reference manual/site binder or file.

9.2.6.4. [redacted]

[redacted]

9.2.6.5. [redacted]

[redacted]

9.2.6.6. Blood Immunophenotypying Substudy (Optional)

A subset of study sites may be selected to perform evaluations of circulating cells before and after dupilumab treatment. Only patients who are not on chronic systemic corticosteroids and not on oral antifungal therapy at baseline will be allowed to participate in the blood immunophenotyping substudy.

Blood will be collected from patients in the substudy. Circulating immune cells, including eosinophils, will be analyzed to assess changes in frequency, activation status, and [redacted]. Collection for the blood immunophenotyping substudy will be performed according to the Schedule of Events in Table 1. The results of the substudy will not be included in the CSR.

9.2.7. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research substudy will be required to consent to this optional substudy before samples are banked in long-term storage. Additional samples for future biomedical research will be collected according to the Schedule of Events in Table 1. These unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research related to the study, as reference samples for other studies, or for other research including development and validation of new assays. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.7.1. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics substudy will be required to consent to this optional substudy before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (pre-dose) but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points indicated in Table 1.

DNA and RNA samples will be collected for the pharmacogenomic analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of ABPA and related diseases. These samples will be single-coded as defined by the ICH guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomics analyses which the sponsor is unable to comply with, samples will not be collected from patients at the site.

Research findings from the optional genomic substudy will not be disclosed to the patient or principal investigator, even if they have implications for a patient's health and management. Genetic results from this substudy are for research purposes only and not for medical diagnosis or for reproductive decision-making.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to dupilumab, other ABPA clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of ABPA, as well as related allergic/atopic diseases, may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or ABPA, asthma, and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the ICF will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and adverse events of special interest [AESIs]) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the follow-up period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **AESIs**; serious and nonserious**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions
  - Systemic hypersensitivity reactions
  - Helminthic infections
  - Any severe type of conjunctivitis or blepharitis
  - Keratitis
  - Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female, during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. For a list of AESIs, see Section 10.1.3.

10.2.4. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade):

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double-blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses

- Response to dechallenge (drug discontinuation) or dose reduction, if applicable
- Response to rechallenge (re-introduction of the drug) or dose increase, if applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical/study director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic, cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, ECs or institutional review boards (IRBs), and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug (REGN668; dupilumab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (dupilumab) is assessed against the Reference Safety Information section of the current Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and ECs/IRBs as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Data collected through the implementation of new CRFs regarding the impact of the COVID-19 pandemic on patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety evaluation will be specified in the SAP.

11.1. Statistical Hypothesis

The primary analyses of the study compare the treatment effect of dupilumab 300 mg Q2W against placebo on the absolute change from baseline in pre-bronchodilator FEV1.

The statistical hypotheses to test dupilumab 300 mg Q2W against placebo on having a greater increase from baseline in pre-bronchodilator FEV1 at week 24 are as follows:

- Null hypothesis: $\Delta_{Dupilumab} - \Delta_{Pbo} = 0$
- Alternative hypothesis: $\Delta_{Dupilumab} - \Delta_{Pbo} \neq 0$

where $\Delta_{Dupilumab}$ and Δ_{Pbo} represent the absolute change from baseline in pre-bronchodilator FEV1 at week 24 in the dupilumab and placebo groups, respectively.

11.2. Justification of Sample Size

The power calculation for this study is based on a comparison between dupilumab 300 mg Q2W and placebo with regard to the primary efficacy endpoint of the absolute change from baseline in pre-bronchodilator FEV1 at week 24. Assuming a 1:1 randomization ratio, a standard deviation (SD) for the change from baseline in pre-bronchodilator FEV1 at week 24 of [redacted] in both groups, a 2-sided Type 1 error of 0.05, and a dropout rate of [redacted] by week 24, with approximately 60 randomized patients (~30 patients per group), the study will have approximately 96% power to detect a difference of [redacted] in the change from baseline in pre-bronchodilator FEV1 at week 24 between the dupilumab and placebo groups, based on the 2-sample t-test. [redacted].

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients. It is based on the treatment allocated (as randomized), regardless of whether the treatment kit was used or not. Efficacy endpoints will be analyzed using the FAS.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing drug concentration result following the first dose of study drug.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received any study drug and who had at least 1 non-missing ADA result following the first study dose.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA-negative are set to negative in the NAb analysis set).

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical data, frequencies and percentages will be displayed for each category.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Primary Efficacy Analysis

The absolute change from baseline in pre-bronchodilator FEV1 at week 24 will be analyzed using a mixed-effects model with repeated measures (MMRM) approach. The vector of responses will consist of the absolute change from baseline in pre-bronchodilator FEV1 at weeks 2, 4, 8, 12, and 24. For patients who discontinue study treatment prior to week 24, any off-study treatment pre-bronchodilator FEV1 values collected after the discontinuation of study treatment through week 24 will be included in the analysis. The MMRM model will include OCS use at screening, OAF use at screening, region, age, sex, height, baseline eosinophil count, treatment, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV1 value, and baseline pre-bronchodilator FEV1 value-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the correlations between repeated measurements. Parameters will be estimated using the restricted maximum likelihood (REML) method and the Newton-Raphson algorithm. Statistical inference for the treatment comparison of the absolute change from baseline in pre-bronchodilator FEV1 at week 24 will be derived from the MMRM model using the Kenward Roger method for calculation of the denominator degrees of freedom for the tests of the fixed effects. If the model does not converge, alternative model specifications (eg, a different covariance structure or reduction in the number of covariates) will be applied; details will be provided in the SAP.

For the primary estimand of interest for the primary endpoint, the intercurrent events, strategies, and the corresponding missing data handling approaches are provided as below:

Primary Efficacy Endpoint	**Intercurrent event(s) handling strategies**	**Missing data handling approaches**
Change from baseline in pre-bronchodilator FEV1 at week 24	The intercurrent events will be handled using the **treatment policy strategy** as follows: - Taking rescue medications with systemic corticosteroids and/or oral antifungal drugs (including an increase in dose) for asthma or ABPA for any reason: all endpoint data collected after use of rescue medication will be used in the analysis - Taking prohibited medications: all endpoint data will be included in the analysis irrespective of use of prohibited medications - Discontinuing the study treatment: all endpoint data collected after discontinuation will be used in the analysis	**Two types of missing data:** 1) Patients discontinuing from the study prior to the analysis time point (week 24) will have missing data from the time of discontinuation through week 24; 2) Some intermittently missing data are expected because of occasionally missing a study visit while continuing with the randomized treatment **Missing data handling:** for both types of missing data, the primary analysis MMRM model assumes that missing data are MAR, that is, that patients with missing data would have efficacy outcomes like those in similar patients in their treatment group who continue their randomized treatment through the time point at which data are missing

Sensitivity Analyses

Sensitivity analyses, such as tipping point analyses, may be conducted. Details of the analyses will be specified in the SAP.

Subgroup Analyses

Subgroup analysis will not be performed due to the small study sample size.

11.4.4. Control of Multiplicity

Control of multiplicity is not applicable.

11.4.5. Safety Analysis

The summary of safety results will be presented by treatment group. All safety analyses will be performed on the SAF.

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to prior to the first dose of study drug.
- The on-treatment period is defined as the time from day 1 (on or after administration of the first dose of study drug) to the date of last dose of study drug +14 days or the date of patient last contact, whichever is earlier
- The follow-up period is defined as the time from the date of last dose of study drug +15 days to the EOS visit or the date of patient last contact, whichever is earlier

The treatment-emergent period is comprised of the on-treatment and follow-up periods.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs related to treatment presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a PCSV at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out-of-laboratory range values.

12-Lead ECG

Summaries of 12-lead ECG parameters by treatment will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of patients with PCSV
- ECG status (ie, normal or abnormal); abnormal ECG status will be classified as clinically significant or non-clinically significant

Listings will be provided with flags indicating the PCSV values and ECG status.

11.4.5.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment group and calculated as:

(Date of last study drug administration – date of first study drug administration) + 14 days

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, mean, SD, minimum, Q1, median, Q3, and maximum.

11.4.5.4. Treatment Compliance

The compliance with study drug will be calculated as follows:

Treatment Compliance =

(Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) x 100%

The treatment compliance will be presented by specific ranges. The ranges of interest will be specified in the SAP.

11.4.5.5. Analysis of Drug Concentration Data

The concentrations of functional dupilumab over time will be summarized by descriptive statistics.

No formal statistical hypothesis testing will be performed.

11.4.6. Analysis of Immunogenicity Data

Immunogenicity will be characterized into ADA and NAb responses as described below:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
- Treatment-boosted ADA response, defined as any post-dose positive ADA assay response that is 4-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay depending on the study

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient, time point, and dose cohort will be provided. Incidence of treatment-emergent ADA, persistent response, and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.4.7. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Data analyses of biomarkers (Section 5.6) will be described in the SAP, and the results will be described in the CSR.

11.5. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical/surgical history, and spirometry) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – assign screening IDs, randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record, and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient's final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

ADULT PATIENTS:

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

PEDIATRIC PATIENTS:

The principles of informed consent are described in ICH guidelines for Good Clinical Practice.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the

parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents'/guardians' consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients and their parent(s) or legal guardian(s) must be informed of the new information and provide their written consent if they wish the patient to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s).

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter, with a current list of the IRB/EC members and their functions, must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study is enrolled earlier than expected

In all cases, the appropriate IRB/EC and health authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Allergic Bronchopulmonary Aspergillosis" and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX A. ORAL CORTICOSTEROIDS (OCS) DOSE REDUCTION SCHEDULE DURING THE RANDOMIZED TREATMENT PERIOD FOR PATIENTS WHO ENTER THE STUDY ON OCS AT BASELINE

The OCS dose should be down-titrated during this phase following a predetermined schedule that is based upon the OCS dose patient was receiving at baseline visit (week 0). During this period, patients will continue taking their background controller medication(s) (ICS +/- LABA, LTRA, LAMA, theophylline, etc) without any changes. The reduction in OCS dose should occur per the schedule unless the patient meets defined criteria indicating that it is not acceptable for the patient to reduce the dose. A clinical assessment should be completed prior to each dose reduction. Primary reasons for not following the scheduled dose reduction include:

1. FEV1 >15% reduction from the baseline value
2. Need for rescue short-acting bronchodilator medication by metered dose inhaler or dry powder inhaler use more than 4 puffs/day (or 2 or more nebulized doses/day) above the mean baseline value for any 2 consecutive days in the prior week; or 12 puffs or more of a short-acting bronchodilator metered dose inhaler or dry powder inhaler (or more than 6 uses of a nebulizer) on any 1 day in the prior week
3. Increase in ACQ-5 score ≥+0.5 from the prior OCS dose assessment visit
4. Clinically significant respiratory exacerbation
5. Requiring hospitalization or treatment in the ED/urgent care due to asthma related or ABPA-related symptoms
6. Clinically significant event, based on investigator judgment, that requires treatment by OCS dose adjustment

The investigator will decide, depending on the reason for not reducing the OCS dose per schedule, whether to maintain or increase patient's current OCS dose by 1 step.

Table 2: [redacted]

Table 3: [redacted]

[redacted]

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Allergic Bronchopulmonary Aspergillosis

Protocol Number: R668-ABPA-1923

Protocol Version: R668-ABPA-1923 Amendment 4

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00295189 v1.0

Approval/eSignature	[redacted] 24-Mar-2023 14:52:11 GMT+0000

Approval/eSignature	[redacted] 24-Mar-2023 15:11:00 GMT+0000

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