STATISTICAL ANALYSIS PLAN
VERSION: 1.0

Clinical Study Protocol Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DUPILUMAB IN PATIENTS WITH ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS
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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

$\Delta_{FEV1\_24\_Dupi}$	Mean absolute change from baseline in pre-bronchodilator FEV1 at Week 24 in the dupilumab group
$\Delta_{FEV1\_24\_Pbo}$	Mean absolute change from baseline in pre-bronchodilator FEV1 at Week 24 in the placebo group
AAS	Anti-drug Antibody Analysis Set
ABPA	Allergic bronchopulmonary aspergillosis
ACQ-5	Asthma Control Questionnaire 5-item version
ADA	American Diabetes Association
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
A fumigatus	*Aspergillus fumigatus*
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCA	Antineutrophil cytoplasmic antibodies
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BDM	Biostatistics and Data Management
BMI	Body mass index
BUN	Blood urea nitrogen
CCG	Clinical completion guideline
[redacted]	[redacted]
CI	Confidence interval
CK	Creatine kinase
CMQ	Custom MedDRA® query
CPK	Creatine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CT	Computed tomography
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury

ECG	Electrocardiography
eCRF	Electronic case report form
ED	Emergency department
EOS	End of study
EOT	End of treatment
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
[redacted]	[redacted]
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antigen antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HLT	High level term
HR	Heart rate
[redacted]	[redacted]
HRQoL	Health-related quality of life
HU	Hounsfield units
ICF	Informed consent/assent form
ICS	Inhaled corticosteroids
IFN-γ	Interferon gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL4R	Interleukin-4 receptor
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
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LTRA	Leukotriene receptor antagonist
MAR	Missing at random
MCMC	Markov-chain Monte Carlo
MedDRA®	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model with repeated measures
NAb	Neutralizing antibody
NAS	Neutralizing Antibody Analysis Set
OAF	Oral antifungals
OCS	Oral corticosteroids
OLS	Ordinary least squares
PCSV	Potentially clinically significant value
[redacted]	[redacted]
pH	Potential of hydrogen
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PR	P wave, R wave
PRO	Patient-reported outcome
PT	Preferred term
Q1	First quartile
Q2W	Every 2 weeks
Q3	Third quartile
QRS	Q wave, R wave, S wave
QT	Q wave, T wave
QTcB	Corrected QT interval by Bazett's formula
QTcF	Corrected QT interval by Fredericia's formula
RBC	Red blood cells
Ref	Reference
REML	Restricted maximum likelihood
SABA	Short-acting bronchodilator

SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
SBP	Systolic blood pressure
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SGRQ	St. George's Respiratory Questionnaire
SI	Standard international
SLIT	Sublingual immunotherapy
SMQ	Standardized MedDRA® query
SOC	System organ class
[redacted]	[redacted]
TBILI	Total bilirubin
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
WBC	White blood cells
WHO-DD	World Health Organization-Drug Dictionary
WOCBP	Women of childbearing potential

1. OVERVIEW

The statistical analysis plan (SAP) is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses, and analysis presentation to be used for the study specified in protocol R668-ABPA-1923 amendment 4, dated March 24, 2023.

1.1. Study Description and Objectives

This is a phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dupilumab in patients with allergic bronchopulmonary aspergillosis (ABPA) who meet modified International Society for Human and Animal Mycology (ISHAM) working group 2013 criteria for ABPA. Approximately 60 patients will be enrolled in the study and randomized in a 1:1 ratio to receive either dupilumab 300 mg subcutaneously (SC) every 2 weeks (Q2W) or placebo SC Q2W for a minimum of 24 weeks and a maximum of 52 weeks.

1.1.1. Primary Objectives

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

1.1.2. 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 immunoglobulin E (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

1.1.3. Exploratory Objectives

The exploratory objectives of the study are:

[redacted]

1.2. 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 forced expiratory volume in 1 second (FEV1).

The statistical hypotheses to test dupilumab 300 mg Q2W against placebo with respect to pre-bronchodilator FEV1 at Week 24 are as follows:

- Null hypothesis: $\Delta_{FEV1\_24\_Dupi} - \Delta_{FEV1\_24\_Pbo} = 0$
- Alternative hypothesis: $\Delta_{FEV1\_24\_Dupi} - \Delta_{FEV1\_24\_Pbo} \neq 0$

where $\Delta_{FEV1\_24\_Dupi}$ and $\Delta_{FEV1\_24\_Pbo}$ represent the mean absolute change from baseline in pre-bronchodilator FEV1 at Week 24 in the dupilumab and placebo groups, respectively.

1.3. Interim Analysis/(es)

No interim analysis is planned.

1.4. Modifications from the Statistical Section in the Final Protocol

Only a single set of potentially clinically significant values (PCSV) tables will be provided for each applicable safety category (e.g., laboratory tests, electrocardiography, and vital signs). As the PCSV criteria defined in Section 14.3 are primarily defined in terms of changes from baseline, separate tables for patients in whom the PCSV criterion was normal or missing at baseline are not applicable.

Only listings required for the clinical study report will be produced.

In the definition of the on-treatment period for safety variables, mention of the date of patient last contact was removed; this text is not applicable as the date of patient last contact cannot be prior to the date of the last adverse event reported for an individual patient. In addition, the definition of the follow-up period for safety variables was modified to ensure a consistent reporting window for all patients.

1.5. Revision History for SAP Amendments

This is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design

This phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of dupilumab is designed to evaluate the efficacy and safety of dupilumab in adult and adolescent (≥12 years of age) patients with ABPA who meet modified ISHAM working group 2013 criteria for ABPA. Approximately 60 patients will be enrolled in the study. The study consists of 3 study periods:

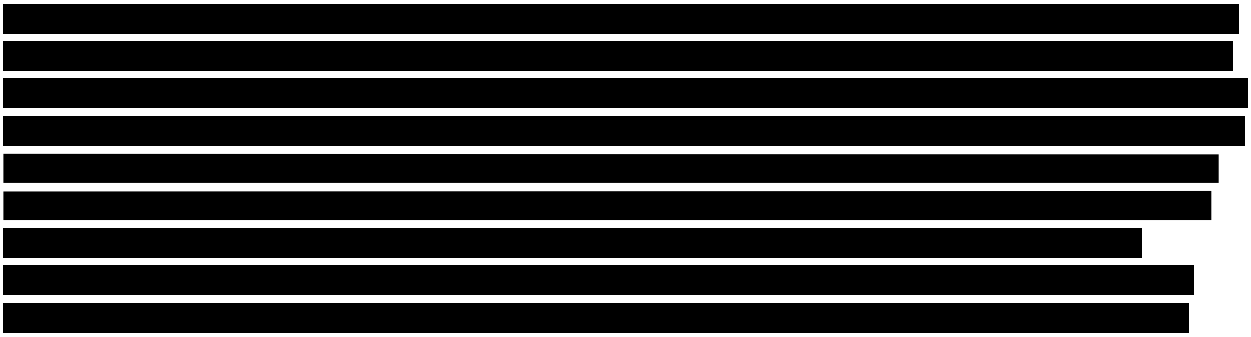
- Screening period (4 weeks)
- Randomized treatment period (24-52 weeks)
- Post-treatment follow-up period (12 weeks)

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: Asia, Eastern Europe, Western Countries), chronic systemic corticosteroid use at screening (yes, no), and oral antifungal (OAF) use at screening (yes, no). Per protocol, patients on oral corticosteroids (OCS) 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.

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 (inhaled corticosteroids [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 (e.g., changes to background asthma controller medication or initiation of antifungal therapy) may be made at the investigator's discretion.



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.

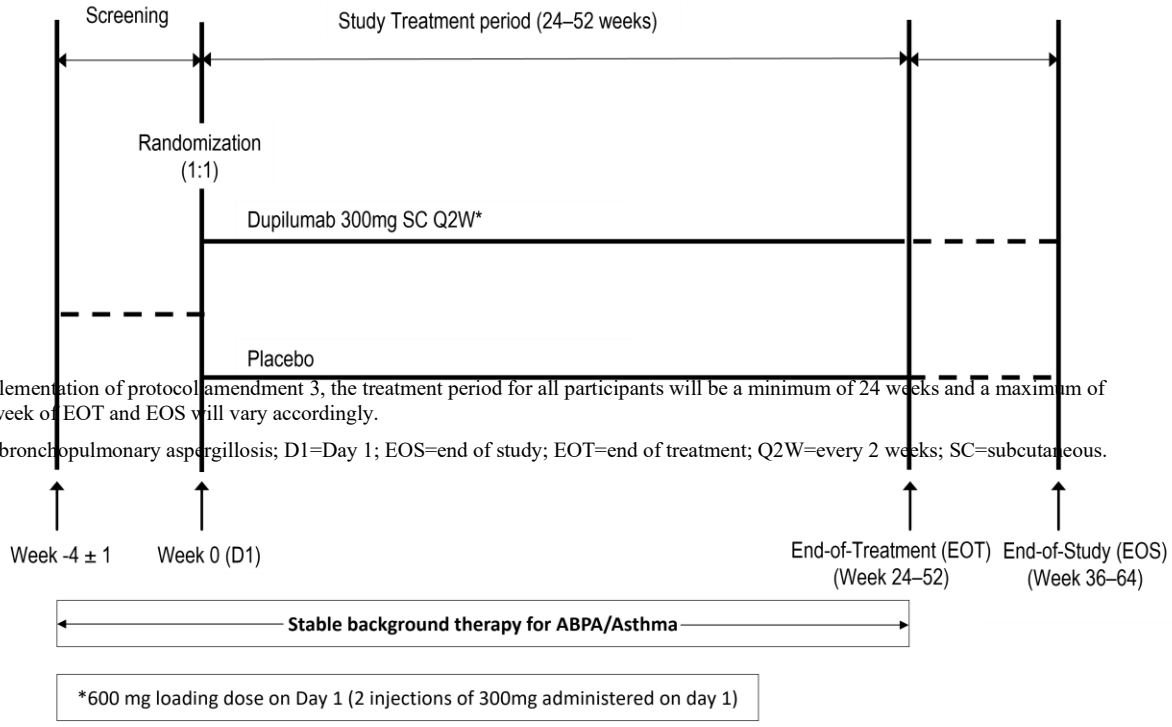
For patients receiving OAF therapy during the treatment period, the dose and regimen of the OAF agent should remain stable until the end of the treatment period. However, antifungal discontinuation or modification to the dose or regimen is permitted for the following reasons: side effects, intolerance,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

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.

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 applicable remaining study visits and participate in all safety follow-up assessments according to the visit schedule (see Section 14.2).

Presented below is the study flow diagram depicting the different periods of the study. Study assessments and procedures (including treatment administrations) are presented by study period and scheduled visit in the Schedule of Time and Events in Section 14.2.

Figure 1: Study Flow Diagram



Note: Upon implementation of protocol 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.

ABPA=allergic bronchopulmonary aspergillosis; D1=Day 1; EOS=end of study; EOT=end of treatment; Q2W=every 2 weeks; SC=subcutaneous.

2.2. Sample Size and Power Considerations

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 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. The power was calculated via a 2-sample t-test using [redacted] software.

[redacted]

3. ANALYSIS SETS

The following defines the sets of patients whose data will be used for statistical analysis.

3.1. Full Analysis Set

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.

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). "As treated" is defined as follows:

- If a patient receives at least 1 dupilumab injection during the study, the patient will be assigned to the dupilumab 300 mg Q2W treatment group in all analyses on the SAF population, regardless of the treatment group to which the patient was randomized.
- If a patient receives only placebo injections during the study, the patient will be assigned to the Placebo group in all analyses on the SAF population, regardless of the treatment group to which the patient was randomized.

3.3. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) includes all randomized patients who received any study drug and who had at least one non-missing drug concentration result following the first dose of study drug. The PKAS is based on the treatment received rather than as randomized.

3.4. Immunogenicity Analysis Sets

3.4.1. Anti-drug Antibody Analysis Set

The Anti-drug Antibody (ADA) Analysis Set (AAS) includes all treated patients who received any amount of study drug (active or placebo) and who had at least one non-missing ADA result following the first dose of study drug. The ADA analysis set is based on the treatment received rather than as randomized.

3.4.2. Neutralizing Antibody Analysis Set

The Neutralizing Antibody (NAb) Analysis Set (NAS) includes all treated patients (active or placebo) that are included in the AAS analysis set and that tested negative at all ADA sampling times or tested positive at one or more post-dose ADA sampling times and had at least one non-missing post-dose NAb result (either imputed or analysis result). Samples that tested negative for ADA are not assayed in the NAb assay and the corresponding NAb results are imputed as negative and included as such in the NAS analysis set. Patients in the NAS with multiple post-dose ADA results which consist of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), are set to NAb negative. Patients in the NAS that have at least one post-dose positive NAb analysis result are set to NAb positive even if other NAb results are missing.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary-level statistics for data:

- Continuous variables will be summarized within each treatment group, presenting the following summary statistics: the sample size (i.e., the number of observations with an available value of the variable), arithmetic mean, sample SD, median, minimum, maximum, first quartile (Q1), and third quartile (Q3).
- Categorical data will be summarized within each treatment group by frequency (i.e., the number of observations within each level of the categorical variable in a given treatment group). All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with a natural ordering of the category levels. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size for the respective treatment group. Patients with missing data will be included in calculations of percentages unless otherwise specified.

When stratification information is used in data summaries or analyses (e.g., in summaries of baseline demographic or disease characteristics or when used as covariates in statistical models), region and chronic systemic corticosteroid use at screening will be based on the values entered into the interactive voice response system [IVRS]/interactive web response system [IWRS]. Oral antifungal use at screening will be based on adjudication of the prior medications recorded on the Prior and Concomitant Medications electronic case report form (eCRF) as performed by the clinical team of the Sponsor.

All analyses will pool adult and adolescent participants.

Baseline measurements are defined as the Day 1 (i.e., day of first dose of study drug) value for each parameter. If a Day 1 value is not available for a given parameter, then the most recent screening value will be used as the baseline measurement, when available. For patients who are randomized but not treated, the most recent measurement on or prior to the day of randomization will be used as the baseline measurement.

The following rules will be used to determine the baseline measurement based on collected date and time information:

1. For safety data (e.g., vital signs, electrocardiography, and laboratory), pharmacokinetic (PK) data, ADA data, spirometry data, and FeNO measurements, both the date and time of the measurement will be compared to the date and time of the first dose of study drug to determine the baseline measurement. Baseline measurements are those that occur prior to administration of the first dose of study drug. If the time of the measurement is not available, this data will be considered to be treatment-emergent, that is, occurring after the first dose of study drug, and will not be eligible to be considered for the baseline measurement. If the time of administration of the first dose of study drug is not available, all laboratory, PK, and ADA data occurring on the date of administration of the first dose of study drug will be considered to be treatment-emergent and will not be eligible to be

considered for the baseline measurement. If there are multiple Day 1 measurements that are eligible to be considered for the baseline measurement, the most recent value will be considered the baseline measurement (with the exception of spirometry and FeNO data, which have unique rules for handling multiple measurements on the same date as described in Section 7).

2. For all other data, the date of the measurement will be compared to the date of the first dose of study drug (i.e., no time information will be used) to determine the baseline measurement.

For laboratory data, if a measurement falls below the lower limit of quantification (LLOQ) or limit of linearity, half of the lower limit value (e.g., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) or limit of linearity, the upper limit value (e.g., ULOQ) will be used for quantitative analyses.

All data manipulations and analyses will be performed using [redacted]

5. PATIENT DISPOSITION

The number of patients included in and excluded from the FAS, SAF, PKAS, AAS, and NAS analysis sets will be presented by treatment group. Patients excluded from each analysis set will be further summarized by reason for exclusion.

The number of randomized patients with at least one important protocol deviation will be presented by treatment group. Patients with at least one important protocol deviation will be further summarized by deviation category and description of deviation. A separate table will be provided summarizing the number of patients with important protocol deviations due to COVID-19 by treatment group. Corresponding percentages with respect to the number of randomized patients in each treatment group will be provided for these summaries.

5.1. Screening Dispositions

The number of enrolled patients (equivalently, screened patients, that is, patients who signed the informed consent/assent form [ICF]) who are randomized (i.e., assigned a randomization number in the IVRS/IWRS) and the number of enrolled patients who screen-fail (i.e., were not assigned a randomization number in the IVRS/IWRS) will be presented. Patients who screen-fail will be summarized by reason for screen-failure (including COVID-19-related reasons). If applicable, the number of patients who are improperly randomized (i.e., did not meet all inclusion criteria or met one or more exclusion criteria yet were assigned a randomization number in the IVRS/IWRS) will also be displayed. The corresponding percentages with respect to the total number of enrolled patients will also be presented.

5.2. Treatment Period Dispositions

The disposition of all randomized patients during the treatment period will be displayed by treatment group (as randomized). The number of treated patients (i.e., patients who received at least 1 dose of study drug) and the number of patients who complete the treatment period will be presented. A patient is considered to have completed the treatment period if they have an end of treatment (EOT) visit. As patients who discontinue study drug are allowed to remain in the study, the number of treatment period completers who remained on study drug throughout the entirety of the treatment period and those who permanently discontinued study drug early will be reported. Patients who permanently discontinued study drug early will be further summarized by reason for early study drug discontinuation (including COVID-19-related reasons).

The number of treatment period completers who proceed into the follow-up period will be reported. A patient will be considered to have entered the follow-up period if they had an EOT visit and the patient's date of last contact is after the date of the EOT visit. The disposition of patients who enter the follow-up period is described in Section 5.3.

Lastly, the number of patients who discontinue from the study during the treatment period (i.e., who have an early termination visit and no EOT visit in the database) will be presented. Patients who discontinue from the study early will be further summarized by reason for early discontinuation from the treatment period (including COVID-19-related reasons).

Corresponding percentages with respect to the number of randomized patients in each treatment group will also be presented for the aforementioned treatment period disposition statuses.

5.3. Follow-up Period Dispositions

For patients who complete the treatment period and enter the follow-up period (as defined in Section 5.2), the number of patients who complete the follow-up period (i.e., have an EOS visit) and those who discontinue from the follow-up period early will be reported. Patients who discontinue from the follow-up period early will be further summarized by reason for early discontinuation from the follow-up period (including COVID-19-related reasons). Corresponding percentages for these follow-up period disposition statuses will also be provided, using the number of randomized patients who completed the treatment period and entered the follow-up period in each treatment group as the denominator.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized descriptively by treatment group and overall (i.e., all patients combined) for the FAS population:

- Age (years) at screening
- Age category at screening (<18 years, ≥18 years to <40 years, ≥40 years to <65 years, ≥65 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Region (Asia, Eastern Europe, Western Countries)
- Baseline weight (kg)
- Baseline weight category (<60 kg, ≥60 kg)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m^2)
- Baseline BMI category (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2)

6.2. Screening/Baseline Disease Characteristics

The following disease characteristics will be summarized descriptively by treatment group and overall for the FAS population:

- Systemic corticosteroid use at screening (Yes, No)
- OAF use at screening (Yes, No)
- Baseline peripheral eosinophil count ($10^9/L$)
- Baseline peripheral eosinophil count category (<$0.15\times10^9/L$, ≥$0.15\times10^9/L$)
- Baseline peripheral eosinophil count category (<$0.3\times10^9/L$, ≥$0.3\times10^9/L$)
- Baseline FeNO (ppb)
- Baseline FeNO category (<20 ppb, ≥20 to <35 ppb, ≥35 ppb)
- Baseline pre-bronchodilator FEV1 (L)
- Baseline pre-bronchodilator FEV1 category (≤1.5 L, >1.5 L)
- Baseline pre-bronchodilator percent predicted FEV1 (%)
- Baseline pre-bronchodilator percent predicted FEV1 category (<50%, ≥50%)
- [redacted]
- [redacted]
- [redacted]

- Baseline FEV1 reversibility (L)
  - Baseline FEV1 reversibility will be derived as baseline post-bronchodilator FEV1 minus baseline pre-bronchodilator FEV1
- Baseline percent FEV1 reversibility (%)
  - Baseline percent FEV1 reversibility will be derived as (baseline post-bronchodilator FEV1 minus baseline pre-bronchodilator FEV1) divided by baseline pre-bronchodilator FEV1 and multiplied by 100
- [redacted]
- [redacted]
- Baseline serum total IgE (IU/mL)
- Baseline Asthma Control Questionnaire 5-item version (ACQ-5) score
- Baseline St. George's Respiratory Questionnaire (SGRQ) total score
- Number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit (≤1, 2, >2, Unknown, Missing)
  - For each patient, the number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit will be obtained from the question "Has the subject experienced ≥1 severe respiratory exacerbation requiring treatment with systemic corticosteroids within 12 months prior to the screening visit" and the subsequent follow-up question "If Yes, how many severe respiratory exacerbations required treatment in the past 12 months" on the Medical History eCRF. For patients who answer the initial question as "No", the number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit will be set to 0. For patients who answer the initial question as "Yes", the value entered for the subsequent follow-up question will be the number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit. If the initial question is not answered, but a value is entered for the subsequent follow-up question, the value entered will be the number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit. If the initial question is answered as "Yes" but no value is entered for the subsequent follow-up question, the patient will be categorized as "Unknown". If neither question is answered, the patient will be categorized as "Missing".

6.3. Medical History

Patient medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history event will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall for the FAS population.

7. EFFICACY DATA

Efficacy endpoints will be analyzed using the FAS.

Per protocol, spirometry should be performed prior to administration of study drug and in accordance with American Thoracic Society (ATS)/European Respiratory Society (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.

Description of the selection of the "best" FEV1, [redacted] values for the purposes of the efficacy analyses is provided in Appendix 14.4. Selection of the "best" FeNO value for the purposes of the efficacy analyses is also described in Appendix 14.4. 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.

Unless otherwise specified, statistical testing will be performed using 2-sided tests with a nominal Type 1 error of 0.05. Two-sided confidence intervals (CIs) will be at the nominal 95% level unless otherwise specified.

7.1. Description of Efficacy Data

7.1.1. Pre-bronchodilator FEV1

The measurement used for the primary efficacy analysis is pre-bronchodilator FEV1. Pre-bronchodilator FEV1 is collected at screening, baseline, Weeks 2, 4, 8, 12, 24, 36, 44, and at EOT and EOS. For patients receiving OCS at baseline, pre-bronchodilator FEV1 is also collected at Weeks 6, 10, 14, and 16 when these visits are performed in-clinic.

The primary efficacy endpoint is the absolute change from baseline in pre-bronchodilator FEV1 compared to placebo at Week 24.

7.1.2. Severe Respiratory Exacerbations

Occurrences of severe respiratory exacerbations are recorded during the entirety of the study duration (i.e., from screening through post-treatment follow-up). A severe respiratory exacerbation is 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). Per protocol, the start dates of severe respiratory exacerbation events must occur ≥28 days apart to be considered as distinct events. A secondary efficacy endpoint is the annualized rate of severe respiratory exacerbations over the 24-52-week treatment period.

Another secondary efficacy endpoint is the annualized rate of ABPA-related exacerbations over the 24-52-week treatment period. ABPA-related exacerbations are defined as severe respiratory exacerbations (as defined above) that are associated with a doubling of serum total IgE from the prior pre-exacerbation value. Per protocol, 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. The serum total IgE value from this unscheduled visit (or the next available measurement if the unscheduled visit was not performed or if the blood draw from the unscheduled visit did not result) will be used to determine if a doubling of the serum total IgE from the prior pre-exacerbation value occurred. Only serum total IgE measurements collected within 30 days after the severe respiratory exacerbation (i.e., with date of serum total IgE blood draw – start date of severe respiratory exacerbation event + 1 ≤ 30) will be considered valid for the purposes of determining whether a doubling of serum total IgE occurred. If the serum total IgE measurement is collected beyond 30 days after the severe respiratory exacerbation event or if no post-exacerbation serum total IgE measurement is available, the severe respiratory exacerbation will be considered to be not ABPA-related for the purposes of analysis. The pre-exacerbation value is defined as the value of the most recent IgE measurement collected prior to the start date/time of the severe respiratory exacerbation event.

The annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility over the 24-52-week treatment period is also a secondary efficacy endpoint.

For each of the aforementioned respiratory exacerbation efficacy endpoints, severe respiratory exacerbations will be determined based on the information entered in the Adverse Event eCRF. Specifically, adverse event records with verbatim term that includes the text “severe respiratory exacerbation” will be selected for analysis. To determine whether a severe respiratory exacerbation is ABPA-related, the date/time of each severe respiratory exacerbation event recorded on the Adverse Event eCRF will be used to identify the prior and subsequent serum total IgE measurements. To determine, whether a severe respiratory exacerbation event required hospitalization or observation for >24 hours in an ED/urgent care facility, the information entered in the “Comment” field on the Adverse Event eCRF will be used; sites will enter the text “HEDURG: Yes” into the comment field to indicate severe respiratory exacerbations requiring hospitalization or observation for >24 hours in an ED/urgent care facility, as instructed in the Clinical Completion Guidelines (CCGs).

7.1.3. ACQ-5 Score

The ACQ-5 score is calculated for each patient at each time point of administration as the mean of the first 5 questions on the ACQ patient-reported outcome (PRO) instrument; the ACQ-5 is administered at screening, baseline, Weeks 2, 4, 8, 12, 24, 36, 44, and at EOT and EOS. For patients receiving OCS at baseline, the ACQ-5 is also administered at Weeks 6, 10, 14, and 16 when these visits are performed in-clinic. A secondary PRO endpoint is the absolute change from baseline in the ACQ-5 score over the 24-52-week treatment period.

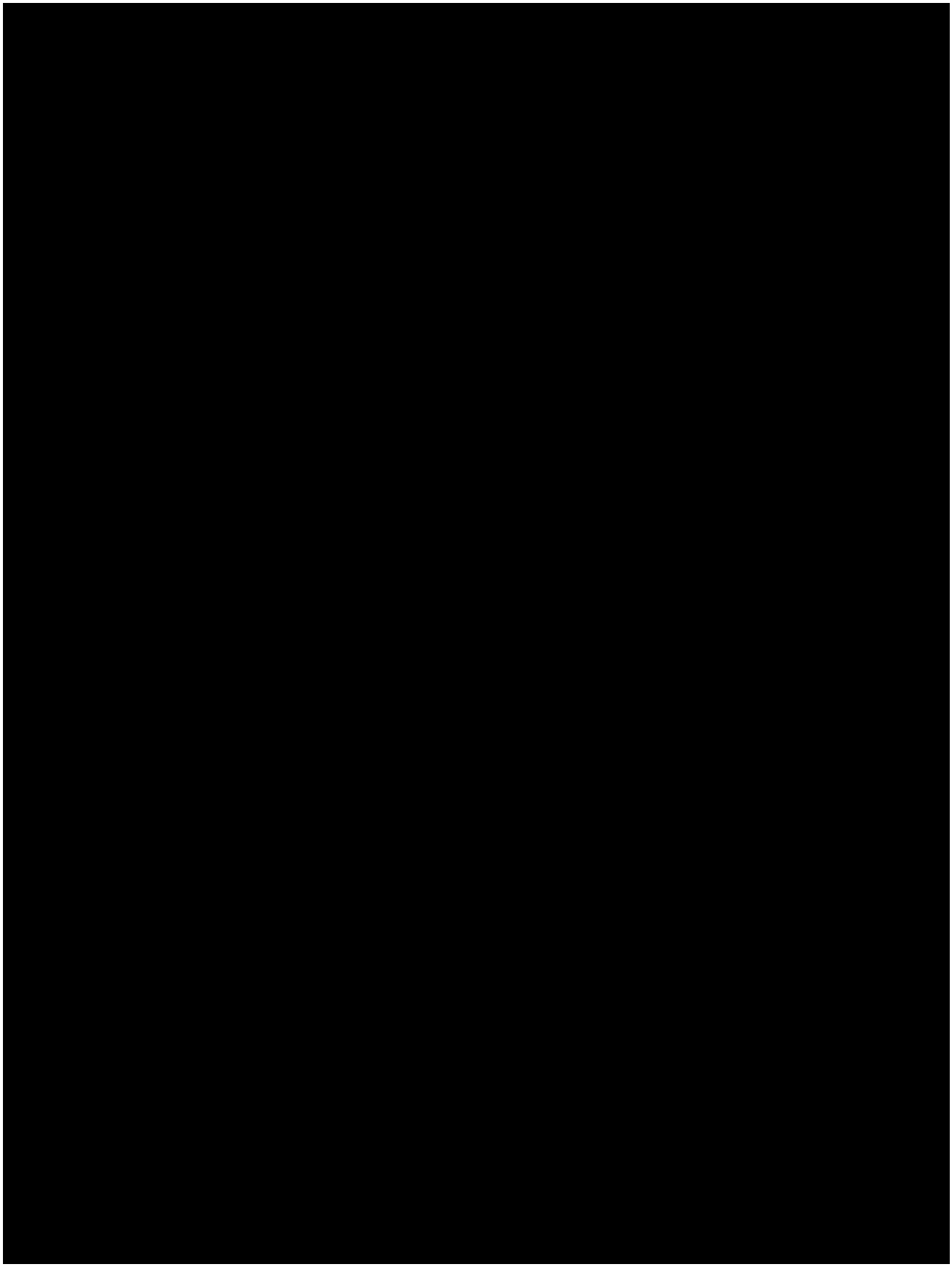
7.1.4. SGRQ Total Score

The SGRQ PRO instrument is administered at baseline, Weeks 4, 12, 24, 36, and at EOT and EOS. Derivation of the total score for each patient at each time point of administration is described in Appendix 14.5. A secondary PRO endpoint is the absolute change from baseline in the SGRQ total score over the 24-52-week treatment period.

The proportion of participants achieving a reduction in the SGRQ total score of ≥4 points from baseline at Weeks 12, 24, 36, and 52 will also be assessed as a secondary PRO endpoint.

7.1.5. Corticosteroid Dose

[redacted]



[redacted]

7.1.6. Pre- and Post-bronchodilator Lung Function Parameters

Pre-bronchodilator lung function parameters including [redacted] are collected at screening, baseline, Weeks 2, 4, 8, 12, 24, 36, 44, and at EOT and EOS. These parameters are also collected for patients on OCS at baseline at Weeks 6, 10, 14, and 16 when these visits are performed in-clinic. [redacted]

[redacted]

7.1.7. Oral Antifungal Use

For patients who are not on oral antifungals at baseline, if 2 or more exacerbations occur during the treatment period, a patient may be initiated on antifungal therapy at the investigator's discretion.

[redacted]

7.1.8. Hospitalizations

Any AEs requiring hospitalization will be recorded on the Adverse Event eCRF. [redacted]

7.1.9. [redacted]

[redacted]

7.1.10. [redacted]

[redacted]

7.1.11. Biomarkers

Serum total IgE is collected at screening, baseline, Weeks 4, 8, 12, 24, 36, and at EOT and EOS. Serum *A fumigatus*-specific IgE is collected at screening, baseline, Weeks 4, 12, 24, 36, and at EOT and EOS. Secondary biomarker endpoints include the percent change from baseline in serum total IgE over the 24-52-week treatment period and the percent change from baseline in serum *A fumigatus*-specific IgE over the 24-52-week treatment period.

FeNO is collected at screening, baseline, Weeks 4, 8, 12, 24, 36, 44, and at EOT and EOS. A secondary biomarker endpoint is the percent and absolute change from baseline in FeNO over the 24-52-week treatment period.

[redacted]

7.1.12. Gene Expression

Patients who are not on chronic systemic steroids and not on antifungal therapy at baseline who provide written informed consent will be eligible to participate in the blood immunophenotyping substudy. Blood samples for the immunophenotyping substudy are drawn at baseline, Week 4, Week 12, and at EOT. [redacted]

7.2. Analysis of Efficacy Data

7.2.1. Analysis of Pre-bronchodilator FEV1

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. As only patients on OCS at baseline will have pre-bronchodilator FEV1 measured at Weeks 6, 10, 14, and 16 (when these visits are performed in-clinic), these time points will not be included in the response vector in the MMRM model to prevent introduction of any potential bias. 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 at screening, sex, height at screening, 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. If this model does not converge, the covariance structure will be modified and additional models run until convergence is achieved. If additional models are needed, the order of the covariance structures will be as follows: heterogeneous autoregressive(1), autoregressive(1), and compound symmetry.

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. The point estimate, 2-sided 95% CI, and p-value for the treatment comparison will be provided. [redacted]

[redacted]

7.2.1.1. Estimand Framework

For the primary efficacy endpoint of the absolute change from baseline in pre-bronchodilator FEV1 at Week 24, intercurrent events may arise as a result of:

i. Taking rescue medications with systemic corticosteroids and/or oral antifungal therapies (including an increase in dose) for asthma or ABPA for any reason

ii. Taking prohibited medications

iii. Discontinuing the study treatment

These intercurrent events will be handled using the treatment policy strategy as follows:

i. All endpoint data collected after the use of rescue medication through Week 24 will be used in the analysis

ii. All endpoint data through Week 24 will be included in the analysis irrespective of the use of prohibited medications

iii. All endpoint data collected after treatment discontinuation through Week 24 will be used in the analysis

There are two ways in which missing data may arise: (i) patients who discontinue from the study prior to Week 24 will have (monotone) missing data from the last contact date through Week 24 and (ii) some intermittently missing data are expected due to patients occasionally missing a study visit or failure to obtain valid spirometry measurements at the study visit. For both types of missing data, the MMRM analysis model assumes that missing data are missing at random (MAR), that is, that patients with missing data at a given time point would have outcomes similar to those of patients in their treatment group with observed data at the given time point.

7.2.1.2. Sensitivity/Supplemental Analyses

A tipping point analysis will be performed as a sensitivity analysis of the primary efficacy endpoint of the absolute change from baseline in pre-bronchodilator FEV1 at Week 24 (provided that the results of the primary analysis described in Section 7.2.1 is statistically significant). The tipping point analysis will be implemented via a pattern-mixture model-multiple imputation approach as described in the steps below:

[redacted]

7.2.2. Secondary and Exploratory Efficacy Analyses

The secondary efficacy endpoint of the annualized rate of severe respiratory exacerbations over the 24-52-week treatment period will be analyzed using a negative binomial regression model. The response variable will be the total number of events occurring during the treatment period. The negative binomial regression model will include OCS use at screening, OAF use at screening, region, number of severe respiratory exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to the screening visit, baseline eosinophil count, and treatment group as covariates. The natural logarithm of the number of days from the date of the first dose of study treatment (or date of randomization for patients who are randomized but not treated) to the date of the EOT visit (or date of last contact for patients who are lost to follow-up or discontinue from the study prior to the EOT visit) divided by 365.25 will be used as the value of the offset variable for each patient. The estimated annualized event rate within each treatment group and the corresponding 2-sided 95% CI will be derived from the model. For patients who permanently discontinue from study treatment, any off-study treatment severe respiratory exacerbation events that occur through the patient's EOT visit (or date of last contact for patients who are lost to follow-up or discontinue from the study prior to the EOT visit) will be included in the analysis. [redacted]

[redacted]

The secondary efficacy endpoints of the annualized rate of ABPA-related exacerbations (i.e., those that are associated with a doubling of serum total IgE from the prior pre-exacerbation value) over the 24-52-week treatment period and the annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility over the 24-52-week treatment period will be analyzed in a similar manner as the

annualized rate of severe respiratory exacerbations. [redacted]. For each of the aforementioned endpoints analyzed via negative binomial regression, if the model fails to converge, only descriptive statistics will be provided for the annualized rate of events in each treatment group.

To evaluate the absolute and/or percent change in the [redacted] efficacy/PRO/biomarker endpoints of the ACQ-5 score, the SGRQ total score, serum total IgE, serum *A fumigatus*-specific IgE, FeNO, [redacted], within-group point estimates of the mean change and corresponding 2-sided 95% CIs (based on the t-distribution) will be provided for each post-baseline time point at which the given parameter is collected (or as otherwise specified in Section 7.1). Patients must have both the baseline and at least 1 post-baseline measurement at the given post-baseline time point to be included in the summary of the mean absolute change/percent change from baseline at the given post-baseline time point. For analyses of percent change from baseline, if a patient's baseline value for a given parameter is 0, that participant will be excluded from the analysis of the given parameter at all post-baseline time points.

Per protocol, FeNO assessments should be conducted prior to spirometry and following a fast of at least 1 hour. For the purposes of the evaluation of the percent and absolute change from baseline in FeNO, FeNO assessments conducted after spirometry or after less than an hour fast will be excluded from the summary. Fasting status is recorded on the FeNO eCRF. For each applicable date, the timing of FeNO measurements will be compared to the timing of spirometry measurements to determine whether the FeNO assessment was conducted prior to spirometry.

To evaluate the secondary PRO endpoint of the proportion of participants who achieve a reduction in the SGRQ total score of ≥4 points from baseline at Weeks 12, 24, 36, and 52, within-group point estimates and 2-sided 95% CIs (based on the Wilson score confidence limits (Wilson, 1927)) will be provided for each of the specified time points. Patients with a baseline SGRQ total score less than 4 points will be excluded from the analysis. Patients must have both the baseline and at least 1 post-baseline measurement at the given post-baseline time point to be included in the calculation of the proportion at the given post-baseline time point.

[redacted]

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

See Section 1.2 and Section 7.2.1 for information related to the hypothesis testing methods used in this study. Control of multiplicity is not applicable.

9. SUMMARY OF EXPOSURE DATA

9.1. Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized by treatment group for the SAF population.

The duration of exposure to study treatment (in days) during the study will be presented by treatment group and calculated for each individual patient as:

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

The calculation does not take into account temporary dosing interruptions (including dosing interruptions due to COVID-19).

The number and percentage of patients randomized and exposed to double-blind study drug will be presented by the following, cumulative, duration of exposure categories: ≥14 days, ≥28 days, ≥42 days, etc., with a 14-day increment added for each subsequent category. The highest category displayed will account for the maximum duration of exposure observed in the study.

In addition, duration of exposure to study treatment during the study will be summarized for each treatment group by the following summary statistics: arithmetic mean, sample SD, minimum, Q1, median, Q3, and maximum.

Compliance with the study drug will be calculated as follows:

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

The number of study drug doses administered and treatment compliance will be summarized for each treatment group by the following summary statistics: arithmetic mean, sample SD, minimum, Q1, median, Q3, and maximum. Treatment compliance will also be presented by the following ranges: <80% and ≥80%.

9.2. Duration of Observation

The duration of observation during the study (in days) will be calculated for each individual patient as:

(Date of last visit – date of first study drug administration) + 1 day

The duration of observation will be summarized descriptively by treatment group for the SAF population via the following summary statistics: arithmetic mean, sample SD, minimum, Q1, median, Q3, and maximum. In addition, the number and percentage of patients randomized and treated will be presented by the following, cumulative, duration of observation categories: ≥1 day, ≥15 days, ≥29 days, ≥43 days, etc., with a 14-day increment added for each subsequent category. The highest category displayed will account for the maximum duration of observation observed in the study.

9.3. Prior and Concomitant Medications

For each participant, medications will be recorded from the date of informed consent/assent through the end of the study (i.e., the EOS visit or, for participants who do not complete the EOS visit, the last available study visit). Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

Prior medications are defined as any medication with start date prior to the date of administration of the first dose of study drug. Per the CCG for this study, all medications given within the 12 months prior to the screening visit will be collected.

Concomitant medications are defined as any medication taken at any time on or after the date of administration of the first dose of study drug through the end of the study. Thus, concomitant medications include (i) medications with start date on or after the date of administration of the first dose of study drug and (ii) prior medications indicated as ongoing or with end date on or after the date of administration of the first dose of study drug. Concomitant medications will be further classified as follows:

- Concomitant medications taken during the 24-52-week treatment period are those medications taken at any time from the date of administration of the first dose of study drug up to the date of the EOT visit (or, if the EOT visit was not performed, the minimum of the date of administration of the last dose of study drug + 14 days and the date of patient last contact).
- Concomitant medications taken during the follow-up period are those medications taken at any time on or after the EOT visit (or, if the EOT visit was not performed, on or after the date of administration of the last dose of study drug + 15 days) through the date of patient last contact.

The number and percentage of patients taking prior/concomitant medications will be summarized, sorted by decreasing frequency of Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4 in the dupilumab treatment group. If a patient has multiple usages of a prior medication or multiple usages of a concomitant medication within the 24-52-week treatment period or within the follow-up period, the medication will be counted only once for the patient for the indicated reporting period. Patients will be counted only once for each medication class (ATC level 2 and 4) associated with a medication. Separate summaries will be provided for prior medications, concomitant medications taken during the 24-52-week treatment period, and for concomitant medications taken during the follow-up period. Summaries of prior medications and concomitant medications taken during the 24-52-week treatment period will be performed on the FAS population. Summaries of concomitant medications taken during the follow-up period will be performed on the subset of the FAS population who completed the treatment period and entered the follow-up period.

Prohibited Medications

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, interferon gamma (IFN-γ), or other biologics) other than protocol-defined use of corticosteroids
- Treatment with an investigational drug (other than dupilumab)
- Initiation of subcutaneous immunotherapy (SCIT), or change in dose for those patients on a stable dose of SCIT within 1 year prior to screening
- Sublingual immunotherapy (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)

Blinded adjudication of prohibited concomitant medications will be performed by the Sponsor clinical team before database lock according to documented procedures.

The number and percentage of patients taking prohibited medications (as adjudicated by the Sponsor clinical team) at any time during the study will be summarized for the FAS population, sorted by decreasing frequency of ATC level 2 and ATC level 4 in the dupilumab treatment group. If a patient has multiple usages of a prohibited medication during the study, the

medication will be counted only once for the patient. Patients will be counted only once for each medication class (ATC level 2 and 4) associated with a medication.

Rescue Medications

Short-acting bronchodilators (SABAs) 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 applicable 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 Time and Events specified in Section 14.2.

Blinded adjudication of rescue medications will be implemented before database lock by considering the type of medication, indication, timing, frequency, and the potential impact of the use of the medication. The rescue medications will be adjudicated by the Sponsor clinical team according to documented procedures.

The number and percentage of patients taking rescue medications (as adjudicated by the Sponsor clinical team) at any time during the study will be summarized for the FAS population, sorted by decreasing frequency of ATC level 2 and ATC level 4 in the dupilumab treatment group. If a patient has multiple usages of a rescue medication during the study, the medication will be counted only once for the patient. Patients will be counted only once for each medication class (ATC level 2 and 4) associated with a medication.

9.4. Prior and Concomitant Procedures

For each participant, procedures will be recorded from the date of informed consent/assent through the end of the study (i.e., the EOS visit or, for participants who do not complete the EOS visit, the last available study visit). Procedures will be coded using the MedDRA® dictionary.

Prior procedures are defined as any procedure performed prior to the date of administration of the first dose of study drug.

Concomitant procedures are defined as any procedure performed at any time on or after the date of administration of the first dose of study drug through the end of the study. Thus, concomitant procedures include (i) procedures with start date on or after the date of administration of the first dose of study drug and (ii) prior procedures indicated as ongoing or with end date on or after the

date of administration of the first dose of study drug. Concomitant procedures will be further classified as follows:

- Concomitant procedures performed during the 24-52-week treatment period are those procedures conducted at any time from the date of administration of the first dose of study drug up to the date of the EOT visit (or, if the EOT visit was not performed, the minimum of the date of administration of the last dose of study drug + 14 days and the date of patient last contact).
- Concomitant procedures conducted during the follow-up period are those procedures conducted at any time on or after the EOT visit (or, if the EOT visit was not performed, on or after the date of administration of the last dose of study drug + 15 days) through the date of patient last contact.

The number and percentage of patients with prior/concomitant procedures will be summarized, sorted by decreasing frequency of primary SOC and PT in the dupilumab treatment group. Separate summaries will be provided for prior procedures, concomitant procedures performed during the 24-52-week treatment period, and for concomitant procedures performed during the follow-up period. If a patient has multiple records of a given prior procedure or multiple records of a given procedure within the 24-52-week treatment period or within the follow-up period, the procedure will be counted only once for the patient for the indicated reporting period. Summaries of prior procedures and concomitant procedures during the 24-52-week treatment period will be performed on the FAS population. Summaries of concomitant procedures during the follow-up period will be performed on the subset of the FAS population who completed the treatment period and entered the follow-up period.

Prohibited Procedures

The following concomitant procedures are prohibited during the study period:

- Major elective surgical procedures
- Bronchial thermoplasty

Blinded adjudication of prohibited concomitant procedures will be performed by the Sponsor clinical team before database lock according to documented procedures.

The number and percentage of patients with prohibited procedures (as adjudicated by the Sponsor clinical team) at any time during the study will be summarized for the FAS population, sorted by decreasing frequency of primary SOC and PT in the dupilumab treatment group. If a patient has multiple records of a given prohibited procedure during the study, the procedure will be counted only once for the patient.

10. ANALYSIS OF SAFETY DATA

Summaries of safety results will be presented by treatment group. All clinical safety variables will be analyzed using the SAF.

For safety variables (i.e., adverse events, laboratory measurements, vital signs, physical examination, and electrocardiography parameters), 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
- The follow-up period is defined as the time from the end of the on-treatment period (i.e., date of last dose of study drug + 15 days) plus 12 weeks (i.e., 84 days)

Additionally, the treatment-emergent period is defined to comprise of the on-treatment and follow-up periods.

To support the assessment of the secondary endpoint of the incidence of treatment-emergent adverse events (TEAEs) from baseline through the end of treatment (week 24-52), summary tables will be provided for AEs that occur during the on-treatment period. A separate set of summary tables will be provided for AEs that occur during the on-treatment or follow-up safety periods (i.e, during the treatment-emergent period).

10.1. Adverse Events

All new or worsening AEs occurring from the time of signing of the ICF through the end of the study will be recorded and coded using the MedDRA® dictionary. The definitions of AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs) are provided in Sections 10.2.1-10.2.3 of the protocol.

Pre-treatment AEs and TEAEs are defined as follows:

- Pre-treatment AEs are AEs that developed or worsened in severity during the pre-treatment period, as defined above.
- TEAEs are AEs that developed or worsened in severity compared to baseline during the on-treatment and follow-up periods, as defined above. As only new AEs that were not present at baseline and pre-existing AEs that worsen during the on-treatment and follow-up periods will be summarized in this study, all AEs collected during the on-treatment and follow-up periods are considered TEAEs.

Adverse events will be summarized with incidence tables. Adverse event incidence tables will present the number and percentage of patients experiencing an AE within each treatment group, sorted by decreasing frequency of SOC and PT in the dupilumab treatment group. Multiple occurrences of the same event in a patient will only be counted once in the summaries. For tables showing AE severity, if a patient has multiple occurrences of the same PT or SOC, only the worst severity will be counted in the summary.

AE summaries will be presented for the TEAEs. The following summaries for TEAEs will be presented by treatment group:

- Overview of TEAEs, consisting of the number and percentage of participants with any TEAE, with any drug-related TEAE, with any TEAE leading to permanent discontinuation of study drug, with any TEAE resulting in death, with any treatment-emergent SAE, with any treatment-emergent, drug-related SAE, and with any treatment-emergent SAE leading to permanent discontinuation of study drug.
- TEAEs by primary SOC and PT
- TEAEs by primary SOC, high level term (HLT), and PT
- TEAEs by primary SOC, PT, and severity (according to the grading scale in Section 10.2.4 of the protocol)
- TEAEs by primary SOC and PT that occur in ≥5% of patients in either treatment group
- TEAEs related to study drug by primary SOC and PT
- Injection site reaction TEAEs by primary SOC, HLT, and PT
- TEAEs with fatal outcome by primary SOC and PT
- Serious TEAEs by primary SOC and PT
- TEAEs leading to permanent discontinuation of study treatment by primary SOC and PT

10.1.1. Adverse Events of Special Interest

Adverse events of special interest for this study are as follows:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

Summaries of treatment-emergent AESIs by AESI category, primary SOC, and PT using the search criteria specified in Table 1 will be presented.

Table 1: AESI Categories and Corresponding Search Criteria

AESI Category	Search Criteria
Anaphylactic reactions	Narrow SMQ for "Anaphylactic reaction"
Systemic hypersensitivity reactions (excluding events already included under anaphylactic reactions)	Narrow SMQ for "Hypersensitivity" minus narrow SMQ for "Anaphylactic reaction", followed by blinded adjudication by the Sponsor clinical team
Helminthic infections	HLT of "Cestode infections" or "Helminthic infections NEC" or "Nematode infections" or "Trematode infections"
Any severe type of conjunctivitis or blepharitis	(Broad CMQ for "Conjunctivitis" or any PT containing "blepharitis") and with severity recorded as "Severe"
Keratitis	Narrow SMQ for "Corneal disorders"
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	HLT of "Eosinophilic disorders" or PT of "Eosinophil count increased", followed by blinded adjudication by the Sponsor clinical team

Note: PTs included in this table are based on MedDRA® version 26.1. If a more recent version of MedDRA® is available and is used for reporting purposes, the PTs used in the programming logic for the search criteria will be updated accordingly.

AESI=adverse event of special interest; CMQ=custom MedDRA® query; HLT=High Level Term; MedDRA®=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified; PT=preferred term; SMQ=standardized MedDRA® query.

10.2. Laboratory Parameters

Blood chemistry, hematology, urinalysis, and other laboratory testing samples (including pregnancy testing samples) will be analyzed by a central laboratory. Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

The following laboratory tests will be collected and summarized by treatment group according to the time points specified in the Schedule of Time and Events in Section 14.2:

Blood Chemistry

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

Hematology

- Hemoglobin
- Hematocrit
- Red blood cells (RBCs)
- White blood cells (WBCs)
- Red cell indices
- Platelet count

Differential:

- Neutrophils
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

Urinalysis

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

Other Laboratory Tests

Other laboratory tests include:

- Antineutrophil cytoplasmic antibodies (ANCA) at screening
- Hepatitis screen including hepatitis B surface antigen (HBsAg), hepatitis B surface antigen antibody (HbsAb), hepatitis B core antibody (HbcAb), and hepatitis C virus antibody (HCVAb)
- Human immunodeficiency virus (HIV) (anti-HIV-1 and anti-HIV-2 antibodies) serology
- Serum immunoglobulin G (IgG) against *A fumigatus*
- *A fumigatus* skin testing
- Serum *A fumigatus*-specific IgE
- Urine toxicology for drug screening
- Pregnancy test: for women of childbearing potential (WOCBP), pregnancy testing will include a serum pregnancy test at screening and urine pregnancy tests at subsequent time points as specified in the Schedule of Time and Events in Section 14.2.

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

Significantly abnormal test results that occur after the start of study 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 drug 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 of the protocol.

Clinical laboratory analytes will be converted to standard international (SI) units and grouped by function in summary tables. Clinical laboratory values and change from baseline in clinical laboratory values at all scheduled post-baseline assessment time points will be summarized via descriptive statistics by treatment group.

Patient laboratory parameter measurements will be evaluated by PCSV criteria, specifically identifying patients with at least 1 post-baseline measurement that meets the PCSV criteria (see Section 14.3). Patients meeting the PCSV criteria will be summarized by patient count (and percentage) for a post-baseline PCSV measurement by treatment group. When the PCSV definition involves a change from baseline value, patients must have a baseline value to be included in the summaries. All measurements collected during the study, including values from unscheduled visits, will be used in the PCSV analyses.

10.3. Vital Signs

The following vital signs parameters will be recorded and summarized according to the Schedule of Time and Events in Section 14.2:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Body temperature
- Respiratory rate
- Weight

Vital signs values and change from baseline in vital signs values at all scheduled post-baseline assessment time points will be summarized via descriptive statistics by treatment group.

For summaries of body temperature, all measurements will be converted to oral equivalent. If the method of temperature collection is not available, the measurement will not be eligible for inclusion in the summary. Measurements will be converted to oral equivalent as follows:

- axillary temperature + 0.3°C = oral equivalent temperature
- rectal temperature – 0.5°C = oral equivalent temperature
- ear temperature – 0.5°C = oral equivalent temperature

Vital signs measurements will be evaluated by PCSV criteria, specifically identifying patients with at least 1 post-baseline measurement that meets the PCSV criteria (see Section 14.3). Patients meeting the PCSV criteria will be summarized by patient count (and percentage) for a post-baseline PCSV measurement by treatment group.

10.4. Electrocardiography

The following standard 12-lead electrocardiography (ECG) parameters will be recorded and summarized by treatment group according to the Schedule of Time and Events in Section 14.2:

- Mean heart rate
- P wave, R wave (PR) interval
- Q wave, R wave, S wave (QRS) duration
- Q wave, T wave (QT) interval
- QT interval corrected for heart rate using Bazett's formula (QTcB), where QTcB (ms) = QT/$\sqrt{RR}$, QT is the uncorrected QT interval measured in ms, and RR (the elapsed time between 2 successive R waves) is 60/HR with HR being the heart rate in beats per minute.
- QT interval corrected for heart rate using Fridericia's formula (QTcF), where QTcF (ms) = $QT/RR^{1/3}$, QT is the uncorrected QT interval measured in ms, and RR (the elapsed time between 2 successive R waves) is 60/HR with HR being the heart rate in beats per minute.
- RR interval
- Interpretation, i.e., overall ECG status along with findings.

ECG measurements and change from baseline at all scheduled post-baseline assessment time points will be summarized via descriptive statistics by treatment group.

ECG parameters will be evaluated by PCSV criteria, specifically identifying patients with at least 1 post-baseline measurement that meets the PCSV criteria (see Section 14.3). Patients meeting the PCSV criteria will be summarized by patient count (and percentage) for a post-baseline PCSV measurement by treatment group.

Shift tables will be constructed showing patients' transition in ECG status from baseline to specified post-baseline time points by treatment group. ECG status will be categorized as Normal, Abnormal (Not Clinically Significant), or Abnormal (Clinically Significant).

10.5. Other Safety Data

Summaries of COVID-19-related TEAEs (as identified by the Standardized MedDRA® Query (SMQ) for COVID-19 using narrow search criteria) will be presented by treatment group.

Additionally, the following summaries of conjunctivitis adverse events will be presented by treatment group:

- Treatment-emergent conjunctivitis AEs by primary SOC and PT using the Conjunctivitis Custom MedDRA® Query (CMQ) (Broad) search criteria specified in Table 2
- Treatment-emergent conjunctivitis AEs by primary SOC and PT using the Conjunctivitis CMQ (Narrow) search criteria specified in Table 2

Table 2: Additional Search Criteria for Conjunctivitis Adverse Events

Identifier	Search Criteria
Conjunctivitis CMQ (Broad)	CMQ10645 based on the following PTs: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia
Conjunctivitis CMQ (Narrow)	CMQ10644 based on the following PTs: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, and Atopic keratoconjunctivitis
Note: PTs included in this table are based on MedDRA® version 26.1. If a more recent version of MedDRA® is available and is used for reporting purposes, the PTs used in the programming logic for the search criteria will be updated accordingly. CMQ=custom MedDRA® query; MedDRA®=Medical Dictionary for Regulatory Activities; PT=preferred term.	

10.6. Immunogenicity Data

10.6.1. Immunogenicity Variables

The immunogenicity variables include ADA status, NAb status, and titer at nominal sampling times/visits. Serum samples for ADA will be collected at the clinic visits specified in Section 14.2. Samples positive in the ADA assay will be further characterized for ADA titers and for the presence of NAb.

10.6.2. Analysis of Immunogenicity Data

10.6.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 10.6.1 will be summarized using descriptive statistics. Immunogenicity will be characterized per drug molecule by ADA status, ADA category, and maximum titer category observed in patients in the AAS analysis set. For samples confirmed as drug-specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post-baseline ADA titers are reported as less than 4-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post-baseline titer result ≥4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post-baseline result in the ADA assay. Patients that are treatment-emergent will be further sub-categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post-baseline samples separated by at least a 12-week post-baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients

10.6.2.2. Analysis of NAb Data

The absolute occurrence (n) and percent (%) of patients with each NAb status in the NAS analysis set will be provided by treatment group. The NAb status is categorized as follows:

- Negative – Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay
- Positive – Samples tested positive in the NAb assay

10.6.3. Association of Immunogenicity with Exposure, Safety and Efficacy

10.6.3.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to dupilumab will be explored by treatment group. Plots of individual concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category, and NAb status on these profiles.

10.6.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the treatment-emergent period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category in ADA positive patients
- NAb positive

10.7. Pharmacokinetic Data

PK analyses will be performed on the PKAS.

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Section 14.2. PK parameters may include, but are not limited to, C_{trough} and $C_{trough,SS}$.

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab concentrations in serum at each sampling time by dose
- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs. nominal time
- Graphical presentations of individual functional dupilumab concentration in serum vs. actual sampling time
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum

No formal statistical analysis will be performed.

11. DATA CONVENTIONS

11.1. Definition of Baseline for Efficacy/Safety Variables

The definition of baseline measurements for efficacy and safety variables is provided in Section 4.

11.2. Data Conventions

Adverse Events Data Analysis Conventions

Severity

Frequency tables of severity by TEAE will display only the maximum severity experienced by each patient for each unique AE preferred term. If no severities are recorded for a given preferred term for a patient, the severity will be classified as "Missing" in the frequency tables of severity by TEAE.

Adverse Event Start Date

The AE start date will be used for AE classification (i.e., determining whether the AE is treatment-emergent). If the AE start date is not complete, then, in the analysis dataset, the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will be derived to indicate which date component is missing. Note that if the AE start date is not complete, any time information that is available will be ignored for the purposes of analysis (e.g., will not be used to determine if an AE is treatment-emergent).

If the AE start day is missing and the AE start month and year are not missing:

- If the AE start year is the same as the year of the first dose of study drug and the AE start month is the same as the month of the first dose of study drug, then the AE start day is imputed as the day of the first dose of study drug. If this results in a date after the AE end date, impute the AE start date as the AE end date instead.
- Otherwise, impute the AE start day as "01". If this results in a date prior to the date of initial informed consent/assent, the AE start date will be imputed to be the date of initial informed consent/assent instead.
- The imputation flag is set to "D".

If the AE start month is missing and the AE start year is not missing:

- If the AE start year is prior to the year of the first dose of study drug, impute the AE start day and month as the day and month of the initial informed consent/assent.
- If the AE start year is equal to the year of the first dose of study drug, impute the AE start day and month as the day and month of the first dose of study drug. If this results in a date after the AE end date, impute the AE start date as the AE end date instead.
- If the AE start year is after the year of the first dose of study drug, impute the AE start day and month as "01 January".
- The imputation flag is set to "M".

If the AE start year is missing:

- Impute the AE start date as the date of the first dose of study drug. If this results in a date after the AE end date, impute the AE start date as the AE end date instead.
- The imputation flag is set to "Y".

Adverse Event End Date

The general recommendation is to not impute the AE end date. However, since the AE end date will be used in the programming logic for the imputation of the AE start date, the following intermediate steps will be used.

If the AE end day is missing and the AE end month and year are not missing:

- Impute the AE end day as the last day of the month. If this results in a date after the date of last patient contact, impute the AE end date as the date of last patient contact instead.

If the AE end month is missing and the AE end year is not missing:

- Impute the AE end day and month as "31 December". If this results in a date after the date of last patient contact, impute the AE end date as the date of last patient contact instead.

If the AE end year is missing:

- Impute the AE end date as the date of last patient contact.

Only the original character/numeric AE end date recorded in the Adverse Event eCRF will be kept in the final analysis dataset (i.e., imputed AE end dates will not be retained in the final analysis dataset).

Prior and Concomitant Medications Data Analysis Conventions

To determine whether a medication is a prior (i.e., pre-treatment) medication or a concomitant medication (or both), incomplete medication start dates will be imputed to be as early as possible and incomplete medication end dates will be imputed to be as late as possible. If the medication start/end date is not complete, then, in the analysis dataset, the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will be derived to indicate which date component is missing.

Prior Medication Start Date

If the medication start day is missing and the medication start month and year are not missing, impute the medication start day as "01". The imputation flag is set to "D".

If the medication start month is missing and the medication start year is not missing, impute the medication start day and month as "01 January". The imputation flag is set to "M".

If the medication start year is missing, impute the medication start date to be 1 year prior to the date of initial informed consent/assent. The imputation flag is set to "Y".

Note: For medications with missing start year, the general recommendation is to not impute the medication start date. However, to simplify the programming logic, the imputation proposed is aligned with the CCG, which specifies to collect all medications given within 12 months prior to the screening visit.

Prior Medication End Date

If the medication end day is missing and the medication end month and year are not missing, impute the medication end day as the last day of the month. If this results in a date on or after the date of the first dose of study drug, impute the medication end date as the date of the first dose of study drug -1 instead. The imputation flag is set to "D".

If the medication end month is missing and the medication end year is not missing, impute the medication end day and month as "31 December". If this results in a date on or after the date of the first dose of study drug, impute the medication end date as the date of the first dose of study drug -1 instead. The imputation flag is set to "M".

If the medication end year is missing, impute the medication end date as the date of the first dose of study drug -1. The imputation flag is set to "Y".

Concomitant Medication Start Date

The rules for imputing the concomitant medication start date are the same as those described above for imputing the AE start date.

Concomitant Medication End Date

If the medication end day is missing and the medication end month and year are not missing, impute the medication end day as the last day of the month. If this results in a date after the date of last patient contact, impute the medication end date as the date of last patient contact instead. The imputation flag is set to "D".

If the medication end month is missing and the medication end year is not missing, impute the medication end day and month as "31 December". If this results in a date after the date of last patient contact, impute the medication end date as the date of last patient contact instead. The imputation flag is set to "M".

If the medication end year is missing, impute the medication end date as the date of last patient contact. The imputation flag is set to "Y".

Medication Coding Data Analysis Conventions

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2. However, these unencoded ATC level 4 records need to be confirmed with the study data manager and medical director.

Potentially Clinically Significant Values Data Analysis Conventions

Patients who had a post-baseline PCSV but are missing the baseline value will be regarded as having a treatment-emergent PCSV.

11.3. Data for Non-Efficacy Endpoints

Date of First/Last Study Drug Injection

The date of first study drug injection (equivalently, the date of first dose of study drug administered) is the earliest date of study drug injection among the non-missing, non-zero dosing records documented in the Study Drug Administration eCRF.

The date of last study drug injection (equivalently, the date of the last dose of study drug administered) is the latest date of study drug injection among the non-missing, non-zero dosing records documented in the Study Drug Administration eCRF. If a patient's date of last dose is missing or unknown, his/her last visit date (including phone call visits) up to but not including the EOT visit will be substituted.

11.4. Unscheduled Assessments and Assignment of Data to Visit Windows

Unscheduled Assessments

The determination of values for by-visit analyses for both efficacy and safety variables will be based on assessments available from scheduled visits, or from unscheduled visits if the scheduled visit was not performed.

Extra assessments (e.g., laboratory data or vital signs associated with non-protocol-specified visits or obtained in the course of investigating or managing AEs) will be included in data listings, but not in summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries.

Assignment of Data to Visit Windows

Data analyzed by visit (including efficacy, laboratory, vital signs, ECG, ADA, etc.) will be summarized by the study scheduled visits described in the Schedule of Time and Events in Appendix 14.2.

The analysis visit windows are created per the Schedule of Time and Events for each parameter and will only be applied if the data from the study scheduled visits are unavailable. The following general, hierarchical rules will be applied for mapping the unscheduled visits and/or the early termination visit, EOT visit, or EOS visit (which will subsequently be collectively referred to as the "early termination of treatment or study" [ETTS] visit) for each parameter.

Note that the EOT visit is coded as "Week 52/ Visit 28" for all patients, regardless of the variable 24-52-week treatment period.

1. If the ETTS visit falls in an analysis window which already has an observed value of the parameter from the scheduled visit, the ETTS visit will be mapped to the next scheduled visit, provided there is no observed value of the parameter at the next scheduled visit.
2. If there is no observed value of the parameter from the scheduled visit and if both the ETTS visit and 1 or more unscheduled visits of the parameter are available in the same analysis visit window, only the ETTS visit may be mapped to a scheduled visit.
    a. Note: If at least 2 of the EOT, EOS, and early termination visits are available in the same analysis visit window, then the ETTS visit to be mapped to the scheduled visit will be selected in the following hierarchical order: EOT visit, EOS visit, early termination visit.
3. If there is no observed value of the parameter from the scheduled visit and if there is no ETTS visit but 1 or more unscheduled visits of the parameter available in an analysis visit window, then the following rules will be applied to map the unscheduled visit to the scheduled visit:
    b. If there is only 1 unscheduled visit of the parameter in the analysis visit window, it will be mapped to the scheduled visit.
    c. If there are 2 or more unscheduled visits of the parameter in the analysis visit window, the closest unscheduled visit to the target day will be mapped to the scheduled visit. If 2 or more unscheduled visits are equidistant from the target day, with 1 unscheduled visit occurring prior to and 1 unscheduled visit occurring after the target day, the unscheduled visit occurring after the target day will be selected for mapping to the scheduled visit. If there are 2 or more unscheduled visits that occur on the same day closest to the target day, the average of the parameter values will be mapped to the scheduled visit and used for analysis.

The ETTS and unscheduled visits will be mapped to scheduled visits per the analysis visit windows defined in Table 3 based on the study relative day of each parameter. Only ETTS and unscheduled visits that occur within the analysis visit windows defined in Table 3 will be eligible to be mapped to a scheduled visit.

Table 3: Analysis Visit Windows by Parameter for ETTS/Unscheduled Visit Mapping

Week (Scheduled Visit)	Target Day	Visit Window for Analysis Parameters					
		Spirometry, FeNO	ACQ-5	SGRQ, Serum *A fumigatus*-specific IgE, [redacted] Physical Examination	Vital Signs	Serum Total IgE, Hematology, Blood Chemistry, Urinalysis, ECG, [redacted]	Drug Concentration Sample, ADA Sample
0	1	≤1	≤1	≤1	≤1	≤1	≤1
2	15	[2, 22]	[2, 22]		[2, 22]		
4	29	[23, 36]	[23, 36]	[2, 56]	[23, 36]	[2, 43]	
6	43	[37, 50]	[37, 50]		[37, 50]		
8	57	[51, 64]	[51, 64]		[51, 64]	[44, 71]	
10	71	[65, 78]	[65, 78]		[65, 78]		
12	85	[79, 92]	[79, 92]	[57, 113]	[79, 92]	[72, 113]	[2, 126]
14	99	[93, 106]	[93, 106]		[93, 106]		
16	113	[107, 120]	[107, 127]		[107, 140]		
24	169	[121, 197]	[155, 183]	[141, 197]	[141, 197]	[141, 197]	[127, 210]
36	253	[198, 295]	[239, 267]	[225, 280]	[225, 280]	[225, 280]	
44	309	[296, 337]	[295, 323]		[281, 337]	[281, 337]	
52	365	[338, 393]	[351, 379]	[338, 393]	[338, 393]	[338, 393]	[211, 462]

Note: For a given parameter, only the analysis windows corresponding to the visits that will be summarized/analyzed for that given parameter (per Section 7) are applicable.
ACQ-5=Asthma Control Questionnaire 5-item version; ADA=anti-drug antibody; *A fumigatus=aspergillus fumigatus*; [redacted]; ECG=electrocardiography; ETTS=early termination of treatment or study; FeNO=fractional exhaled nitric oxide; [redacted]; IgE=immunoglobulin E; SGRQ=St. George's Respiratory Questionnaire; [redacted].

11.5. Pooling of Categorical Variables for Statistical Analyses

For any analysis models that adjust for the region stratification factor, the regions of Asia and Eastern Europe will be pooled into a single "Non-Western Countries" level.

12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS/(ES)

No interim analysis is planned for this study.

13. REFERENCES

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14. APPENDIX

14.1. Summary of Statistical Analyses

Efficacy/PD Analysis:

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Other Analyses
Primary Endpoint				
Pre-bronchodilator FEV1	FAS	Absolute change from baseline at Week 24	MMRM with OCS use at screening, OAF use at screening, region, age at screening, sex, height at screening, 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 and unstructured covariance matrix	Tipping point analysis implemented via a pattern-mixture model-multiple imputation approach
Secondary Endpoints				
Severe respiratory exacerbations	FAS	Annualized rate of severe respiratory exacerbations over the 24-52-week treatment period	Negative binomial regression with OCS use at screening, OAF use at screening, region, number of severe respiratory exacerbations in the 12 months prior to the screening visit, baseline eosinophil count, and treatment as covariates	
	FAS	Annualized rate of ABPA-related exacerbations over the 24-52-week treatment period	Negative binomial regression with OCS use at screening, OAF use at screening, region, number of severe respiratory exacerbations in the 12 months prior to the screening visit, baseline eosinophil count, and treatment as covariates	
	FAS	Annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility over the 24-52-week treatment period	Negative binomial regression with OCS use at screening, OAF use at screening, region, number of severe respiratory exacerbations in the 12 months prior to the screening visit, baseline eosinophil count, and treatment as covariates	

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Other Analyses
ACQ-5 score	FAS[†]	Absolute change from baseline in the ACQ-5 score at each time point at which the ACQ-5 is administered during the 24-52-week treatment period	t-distribution	
SGRQ total score	FAS[†]	Absolute change from baseline in the SGRQ total score at each time point at which the SGRQ is administered during the 24-52-week treatment period	t-distribution	
	FAS[†] population with baseline SGRQ total score ≥4 points	Proportion of participants who achieve a reduction in the SGRQ total score of ≥4 points from baseline at Weeks 12, 24, 36, and 52	Wilson score confidence limits	
Serum total IgE	FAS[†,‡]	Percent change from baseline in serum total IgE at each time point at which serum total IgE is collected during the 24-52-week treatment period	t-distribution	
Serum *A fumigatus*-specific IgE	FAS[†,‡]	Percent change from baseline in serum *A fumigatus*-specific IgE at each time point at which serum *A fumigatus*-specific IgE is collected during the 24-52-week treatment period	t-distribution	
FeNO	FAS[†,‡]	Percent and absolute change from baseline in FeNO at each time point at which FeNO is collected during the 24-52-week treatment period	t-distribution	
C_{trough}	PKAS	Functional dupilumab concentrations in serum at each sampling time by dose	Descriptive statistics	

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Other Analyses
Exploratory Endpoints				
[redacted]				

Endpoint	Analysis Population	Primary Analysis	Statistical Method	Other Analyses
[redacted]				

† Patients must have both the baseline and at least 1 post-baseline measurement at the given post-baseline time point to be included in the summary at the given post-baseline time point.

‡ For percent change summaries, patients whose baseline value is 0 will be excluded from the summary at all post-baseline time points.

ABPA=allergic bronchopulmonary aspergillosis; ACQ-5=Asthma Control Questionnaire 5-item version; *A fumigatus=aspergillus fumigatus*; [redacted]; [redacted]; ED=emergency department; EOT=end of treatment; FAS=Full Analysis Set; [redacted]; FeNO=fractional exhaled nitric oxide; FEV1=forced expiratory volume in 1 second; [redacted]; IgE=immunoglobulin E; MMRM=mixed-effects model with repeated measures; OAF=oral antifungals; OCS=oral corticosteroids; SGRQ=St. George's Respiratory Questionnaire; [redacted].

14.2. Schedule of Time and 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[aa]	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[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[aa]	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	
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	
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

		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[aa]	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	
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	
[redacted]																														
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]		X																												

		Randomized treatment period**																														
Study Procedure	Screening Visit[a]	Randomization/ Baseline Visit[b]																													**EOT visit**	**EOS visit**	**Unscheduled Visit[z]**
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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[aa]	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	
(optional)																														
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.

Footnotes for the Schedule of Time and 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 25 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.

14.3. Criteria for Potentially Clinically Significant Values (PCSV)

No adolescent participants (i.e., participants <18 years of age) were enrolled in this study. As such, the PCSV criteria defined in the table below reflect the adult population (i.e., ≥18 years of age).

Parameter	PCSV	Comments
Blood Chemistry		
(ALT or AST) and Total Bilirubin	((ALT ≤3 × ULN and AST ≤3 × ULN) or TBILI ≤2 × ULN) at baseline and ((ALT >3 × ULN or AST >3 × ULN) and TBILI >2 × ULN) post-baseline	
Albumin	>25 g/L at baseline and ≤25 g/L post-baseline	
Alkaline Phosphatase (ALP)	≤1.5 × ULN at baseline and >1.5 × ULN post-baseline	
ALT/SGPT	≤3 × ULN* at baseline and >3 and ≤5 × ULN post-baseline ≤5 × ULN at baseline and >5 and ≤10 × ULN post-baseline ≤10 × ULN at baseline and >10 and ≤20 × ULN post-baseline ≤20 × ULN at baseline and >20 × ULN post-baseline	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies.
AST/SGOT	≤3 × ULN* at baseline and >3 and ≤5 × ULN post-baseline ≤5 × ULN at baseline and >5 and ≤10 × ULN post-baseline ≤10 × ULN at baseline and >10 and ≤20 × ULN post-baseline ≤20 × ULN at baseline and >20 × ULN post-baseline	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies.
Blood Urea Nitrogen (BUN)	<17 mmol/L at baseline and ≥17 mmol/L post-baseline	
Chloride	≥80 mmol/L at baseline and <80 mmol/L post-baseline ≤115 mmol/L at baseline and >115 mmol/L post-baseline	
CPK/CK	≤3 × ULN at baseline and >3 and ≤10 × ULN post-baseline ≤10 × ULN at baseline and >10 × ULN post-baseline	
Creatinine	<150 µmol/L at baseline and ≥150 µmol/L post-baseline ≥30% increase from baseline and <100% increase from baseline ≥100% increase from baseline	Benichou C., 1994. 3 independent criteria

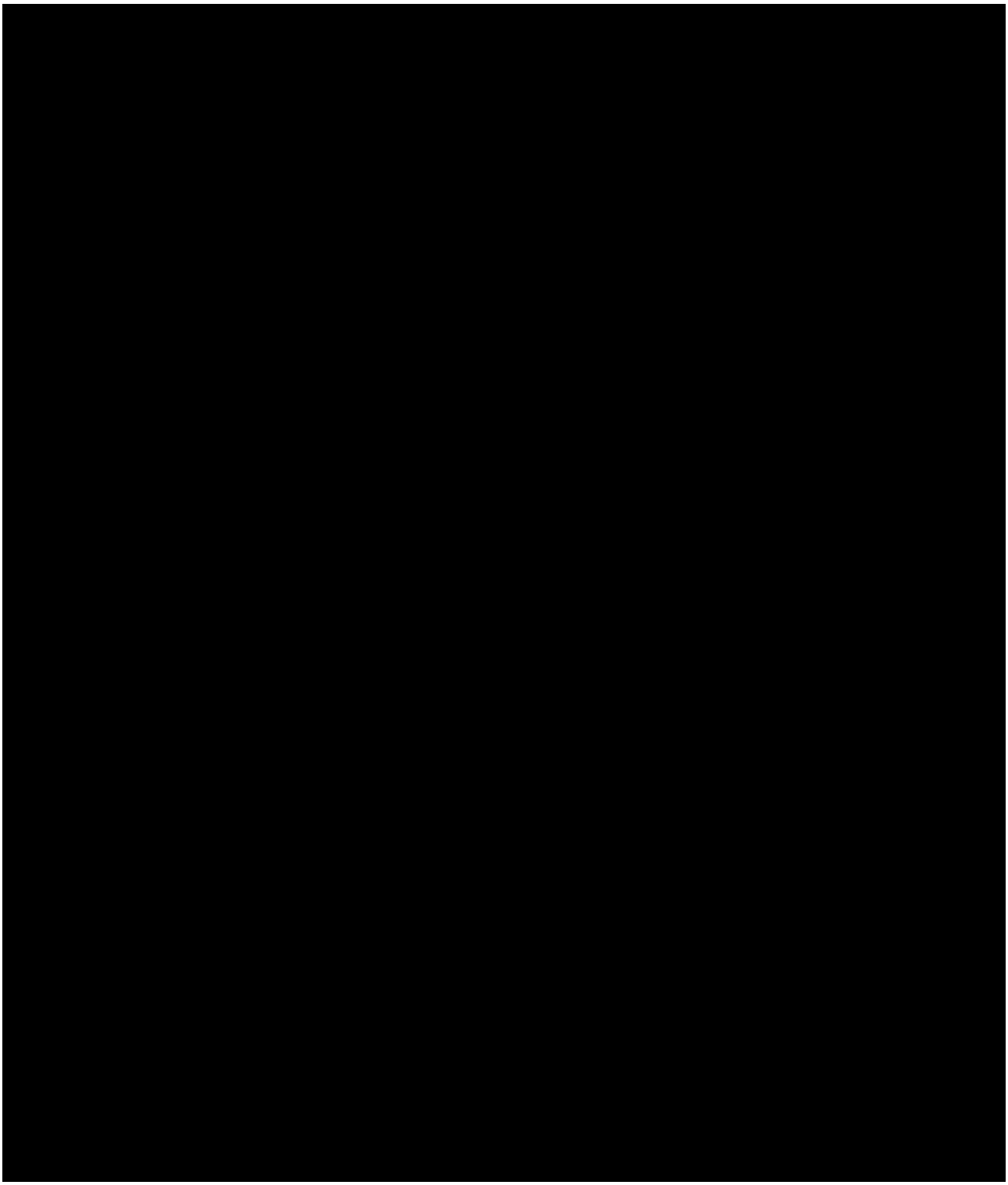
Parameter	PCSV	Comments
Glucose	Hypoglycaemia: (>3.9 mmol/L or ≥LLN) at baseline and (≤3.9 mmol/L and <LLN) post-baseline Hyperglycaemia: <7 mmol/L at baseline (fasted) and ≥7 mmol/L post-baseline (fasted); <11.1 mmol/L at baseline (unfasted) and ≥11.1 mmol/L post-baseline (unfasted)	ADA May 2005. ADA Jan 2008.
Potassium	≥3 mmol/L at baseline and <3 mmol/L post-baseline <5.5 mmol/L at baseline and ≥5.5 mmol/L post-baseline	
Sodium	>129 mmol/L at baseline and ≤129 mmol/L post-baseline <160 mmol/L at baseline and ≥160 mmol/L post-baseline	
Total Bilirubin	≤1.5 × ULN* at baseline and >1.5 and ≤2 × ULN post-baseline ≤2.0 × ULN at baseline and >2 × ULN post-baseline	Must be expressed in ULN, not in µmol/L or mg/L. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies.
Total Cholesterol	<7.74 mmol/L at baseline and ≥7.74 mmol/L post-baseline	Threshold for therapeutic intervention.
Triglycerides	<4.6 mmol/L at baseline and ≥4.6 mmol/L post-baseline	Threshold for therapeutic intervention.
Uric Acid	≥0.12 mmol/L at baseline and <0.12 mmol/L post-baseline ≤0.408 mmol/L at baseline and >0.408 mmol/L post-baseline	
ECG		
HR	≤50 beats per minute post-baseline and decrease from baseline by ≥20 beats per minute ≥120 beats per minute post-baseline and increase from baseline by ≥20 beats per minute	Ref.: CPMP 1997 guideline.
PR	≥220 ms post-baseline and increase from baseline by ≥20 ms	Ref.: CPMP 1997 guideline.
QRS	<120 ms at baseline and ≥120 ms post-baseline	Ref.: CPMP 1997 guideline.
QTcB/QTcF	Borderline: <431 ms at baseline and 431-450 ms post-baseline for Male; <451 ms at baseline and 451-470 ms post-baseline for Female Prolonged: ≤450 ms at baseline and >450 to <500 ms post-baseline for Male; ≤470 ms at baseline and >470 to <500 ms post-baseline for Female <500 ms at baseline and ≥500 ms post-baseline Increase from baseline	Ref.: CPMP 1997 guideline. 5 independent criteria

Parameter	PCSV	Comments
	Borderline: Increase from baseline by 30-60 ms Prolonged: Increase from baseline by >60 ms	
Hematology		
Basophils	≤0.1 Giga/L at baseline and >0.1 Giga/L post-baseline	
Eosinophils	(≤0.5 Giga/L or ≤ULN) at baseline and (>0.5 Giga/L and >ULN) post-baseline	
Hematocrit	>0.37 v/v at baseline and ≤0.37 v/v post-baseline for Male; >0.32 v/v at baseline and ≤0.32 v/v post-baseline for Female <0.55 v/v at baseline and ≥0.55 v/v post-baseline for Male; <0.5 v/v at baseline and ≥0.5 v/v post-baseline for Female	
Hemoglobin	>115 g/L at baseline and ≤115 g/L post-baseline for Male; >95 g/L at baseline and ≤95 g/L post-baseline for Female <185 g/L at baseline and ≥185 g/L post-baseline for Male; <165 g/L at baseline and ≥165 g/L post-baseline for Female Decrease from baseline by ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than those based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Lymphocytes (ALC)	≤4.0 Giga/L at baseline and >4.0 Giga/L post-baseline	
Monocytes	≤0.7 Giga/L at baseline and >0.7 Giga/L post-baseline	
Neutrophils	≥1.5 Giga/L at baseline and <1.5 Giga/L post-baseline (Non-Black); ≥1.0 Giga/L at baseline and <1.0 Giga/L post-baseline (Black)	
Platelets	≥100 Giga/L at baseline and <100 Giga/L post-baseline <700 Giga/L at baseline and ≥700 Giga/L post-baseline	
RBC	≥4 Tera/L at baseline and <4 Tera/L post-baseline for Male; ≥3 Tera/L at baseline and <3 Tera/L post-baseline for Female <7 Tera/L at baseline and ≥7 Tera/L post-baseline for Male; <6 Tera/L at baseline and ≥6 Tera/L post-baseline for Female	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
WBC	≥3.0 Giga/L at baseline and <3.0 Giga/L post-baseline (Non-Black); ≥2.0 Giga/L at baseline and <2.0 Giga/L post-baseline (Black) <16.0 Giga/L at baseline and ≥16.0 Giga/L post-baseline	

Parameter	PCSV	Comments
Urinalysis		
pH	>4.6 at baseline and ≤4.6 post-baseline <8 at baseline and ≥8 post-baseline	Two independent criteria
Vital Signs		
DBP	≤45 mmHg post-baseline and decrease from baseline by ≥10 mmHg ≥110 mmHg post-baseline and increase from baseline by ≥10 mmHg	To be applied for all positions (including missing).
HR/Pulse Rate	≤50 beats per minute post-baseline and decrease from baseline by ≥20 beats per minute ≥120 beats per minute post-baseline and increase from baseline by ≥20 beats per minute	
Respiratory rate	≥12 breaths per minute at baseline and <12 breaths per minute post-baseline ≤20 breaths per minute at baseline and >20 breaths per minute post-baseline	
SBP	≤95 mmHg post-baseline and decrease from baseline by ≥20 mmHg ≥160 mmHg post-baseline and increase from baseline by ≥20 mmHg	To be applied for all positions (including missing).
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared (temporal): >99.0 °F/37.2 °C	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

ADA=American Diabetes Association; ALC=absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; CPK=creatine phosphokinase; CPMP=Committee for Proprietary Medicinal Products; DBP=diastolic blood pressure; DILI=drug-induced liver injury; ECG=electrocardiography; FDA=Food and Drug Administration; Hb=hemoglobin; HR=heart rate; LLN=lower limit of normal; PCSV=potentially clinically significant value; pH=potential of hydrogen; PR=P wave, R wave; QRS=Q wave, R wave, S wave; QT=Q wave, T wave; QTcB=corrected QT interval by Bazett's formula; QTcF=corrected QT interval by Fredericia's formula; RBC=red blood cells; Ref=reference; SBP=systolic blood pressure; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TBILI=total bilirubin; ULN=upper limit of normal; WBC=white blood cells.

14.4. [redacted]



14.5. [redacted]

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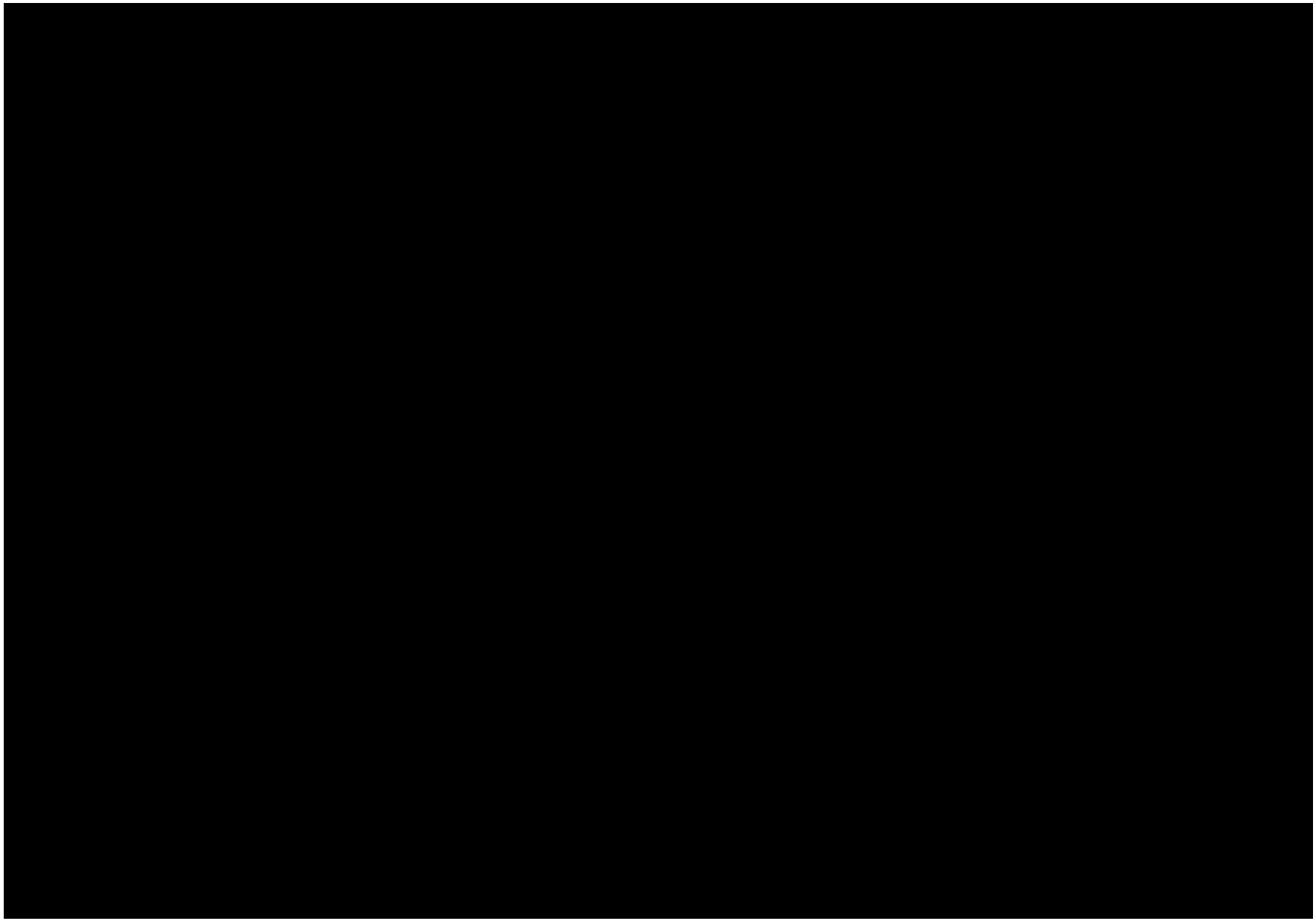

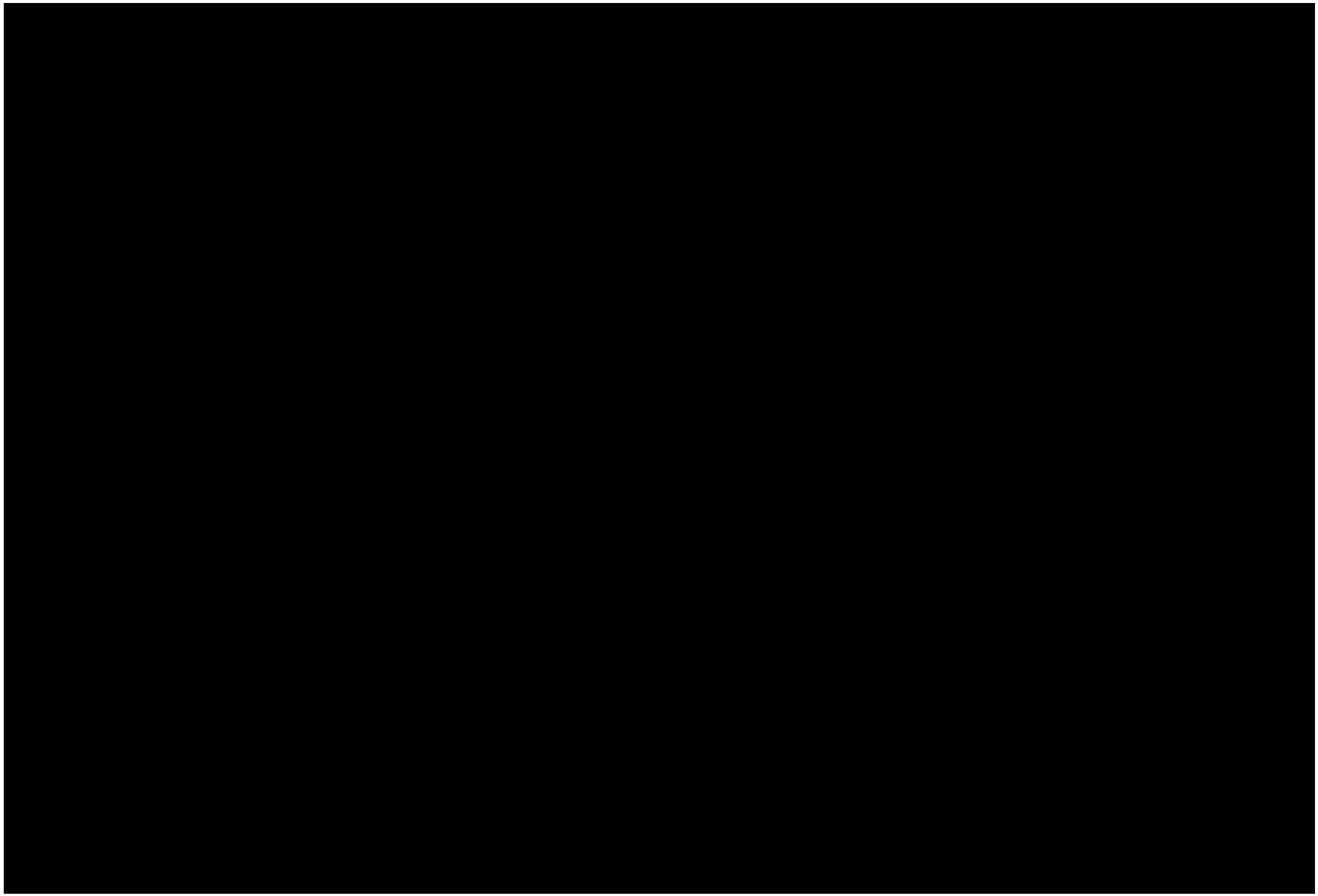

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