STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to assess the efficacy, safety, and tolerability of subcutaneous amlitelimab in adult participants with moderate-to-severe asthma**
Protocol number:	**DRI17509**
Compound number (INN/Trademark):	**SAR445229** **amlitelimab/Not applicable**
Study phase:	**Phase 2**
Short Title:	**Dose ranging study of amlitelimab in adult participants with moderate-to-severe asthma**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**11-May-2024**

Regulatory agency identifier number(s):

IND:	Not applicable
EudraCT/EU-trial number:	2022-000065-41
NCT:	NCT05421598
WHO:	U1111-1272-2612
EUDAMED:	Not applicable
Other:	Not applicable

Date: 11-May-2024 Total number of pages: 89

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VERSION HISTORY

This SAP for study DR17509 is based on the protocol amendment 04 dated 14-December-2023. This section summarizes major changes to the statistical analysis features in the SAP. The first participant was randomized on 14-July-2022. This SAP is approved before the interim analysis is conducted.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	29-Feb-2024	Not Applicable	Original version
2	11-May-2024	Primary analysis for the primary endpoint and key secondary endpoints are changed to use treatment policy; the original primary analysis is included as supplementary analysis.	Per FDA's recommendation.
		Justification and reference studies added for the selection of parameter values in the sample size calculation section	Per FDA's recommendation.

1 INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of statistical strategy and methodology to be used to analyze the data from the randomized, double-blind, placebo-controlled, parallel-group, dose ranging amlitelimab/SAR445229 DRI17509 study.

1.1 STUDY DESIGN

This is a Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to assess the efficacy, safety, and tolerability of add-on therapy with subcutaneous (SC) amlitelimab in adult participants (aged 18-75 years, inclusive) with moderate-to-severe asthma who are not well controlled on ICS plus a second controller medication (eg, LABA, LTRA, methylxanthines, LAMA) with or without oral prednisone for the maintenance treatment of asthma. Participants requiring a third controller are allowed to participate in this study. Study intervention groups are amlitelimab 250 mg with 500 mg loading dose on Day 1, amlitelimab 125 mg with 250 mg loading dose on Day 1, amlitelimab 62.5 mg with 125 mg loading dose on Day 1, or matching placebo, administered during the 60 weeks treatment period.

The primary endpoint is the annualized rate of severe asthma exacerbation events over 48 weeks. Severe exacerbations will be recorded by the Investigator and are defined as either worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days; or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids. For exacerbation events to be counted as 2 separate events, they must be separated by at least 7 days between courses of systemic corticosteroids or doubling of the dose of stable background OCS.

Total of approximately 420 participants will be randomized into the four study intervention groups. Randomization will be stratified by region, screening blood eosinophil count (<300 cells/μL and ≥300 cells/μL), and number of severe asthma exacerbations in the previous 12 months (=1 exacerbation or >1 exacerbations). During the randomization procedure, the eosinophil count at Screening (Visit 1) must be entered in the IVRS/IWRS system. To ensure enrollment according to intended distribution of exacerbation history and eosinophil count, the number of participants enrolled into each stratification group will be controlled and monitored as follows:

- Only 1 severe asthma exacerbation in the previous 12 months: not more than approximately 50% of participants (210 participants).
- Eosinophils <300 eosinophils/μL: not more than approximately 50% of participants (210 participants).

The clinical trial consists of three periods, as outlined below:

- Screening period (up to 4 weeks) to determine whether participants meet entry criteria and to establish level of asthma control before randomization.
  - The screening of a participant triggers the IMP shipment to the site in the IVRS/IWRS system. A maximum of 2 weeks is required to get IMP on site. Randomization of the participant must take this constraint into consideration (allow up to 2 weeks for IMP shipment between screening and randomization).
- Randomized treatment period (60 weeks)
- Follow-up period (12 weeks) to monitor participants after treatment
  - Eligible participants who complete the treatment period will be offered the opportunity to participate in the LTS study with amlitelimab. Participants subsequently enrolled in the LTS study will not participate in the follow-up period of this trial but will have a follow up period after the LTS study.

Participants must have been on existing treatment with medium-to-high doses of ICS therapy (≥500 µg of fluticasone propionate daily or comparable ICS dosage up to a maximum of 2000 µg/day of fluticasone propionate or clinically comparable) in combination with a second controller (eg, LABA, LTRA, LAMA, methylxanthines) for at least 3 months with a stable dose≥1 month prior to Screening (Visit 1) and must stay on their established controller medication for asthma throughout the duration of the study, with the exception of OCS used for maintenance treatment of asthma. The class of reliever medication should not change during the study.

All eligible participants will be randomized (2:2:1:2) to one of the following IMP study intervention groups to be administered for 60 weeks by SC administrations Q4W for the first 6 doses and Q12W thereafter until Week 48:

- Amlitelimab 250 mg with 500 mg loading dose on Day 1
- Amlitelimab 125 mg with 250 mg loading dose on Day 1
- Amlitelimab 62.5 mg with 125 mg loading dose on Day 1
- Matching placebo

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of different doses of amlitelimab compared to placebo in participants with moderate-to-severe, uncontrolled asthma.	• Annualized rate of severe exacerbation events over 48 weeks, defined as: - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of oral corticosteroids (OCS) for the treatment of

Objectives	Endpoints
	asthma, a doubling of the dose for 3 or more days; or - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids
Secondary	
• To evaluate the effects of amlitelimab compared to placebo on lung function as measured by forced expiratory volume in 1 second (FEV1)	• Change from baseline in pre-bronchodilator (BD) FEV1 at Week 48 (**key secondary endpoint)** • Change from baseline in post-BD FEV1 at Week 48 • The absolute change in the percent predicted FEV1 from baseline to Week 48 (pre-BD and post-BD)
• To evaluate the effects of amlitelimab on Asthma Control Questionnaire 5 (ACQ-5)	• Change from baseline in ACQ-5 score at Week 48 (**key secondary endpoint**) • Change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 24, 36, and 60
• To evaluate the effects of amlitelimab on time to first severe exacerbation event	• Time to first severe exacerbation event
• To evaluate the effects of amlitelimab on other spirometry assessments	• Change from baseline in pre-BD and post-BD FEV1 and other lung function measurements (peak expiratory flow [PEF], forced vital capacity [FVC], and forced expiratory flow [FEF] 25-75%) at each spirometry endpoint
• To evaluate the effects of amlitelimab on fraction of exhaled nitric oxide (FeNO)	• Change from baseline in FeNO at Weeks 2, 4, 8, 12, 16, 24, 36, 48 and 60
• To evaluate the effects of amlitelimab compared to placebo on reducing the incidence of "loss of asthma control" (LOAC) events	• Annualized rate of LOAC events, during 48 weeks of treatment, defined by one or several of the following criteria: - A 30% or greater reduction from baseline in morning PEF on 2 consecutive days - $\geq$6 additional reliever puffs of short-acting beta 2-agonists (SABA) OR ≥4 additional puffs of low-dose ICS/formoterol in a 24-hour period (compared to baseline) on 2 consecutive days - Increase in ICS $\geq$4 times than the Visit 2 dose - Worsening of asthma requiring the use of systemic corticosteroids for ≥3 days or, in the case of a stable maintenance regimen of OCS for the treatment of asthma, a doubling of the dose for 3 or more days - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids severe exacerbation event
• To evaluate the effects of amlitelimab on time to first LOAC event	• Time to first LOAC event
• To evaluate the effects of amlitelimab on asthma symptoms	• Change from baseline in the Asthma Daytime Symptom Diary (ADSD) 6-item daily morning score and in the Asthma Nighttime Symptom Diary (ANSD) 6-item daily evening scores at Weeks 2, 4, 8, 12, 24, 36, 48, and 60

Objectives	Endpoints
• To evaluate the effects of amlitelimab on reducing the incidence of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit	• Annualized rate of severe asthma exacerbations requiring hospitalization or emergency room or urgent care visit during 48 weeks of treatment
• Assess the effect of amlitelimab on BD therapy	• Change from baseline in the numbers of inhalations/day of SABA or low-dose ICS/formoterol for symptom relief at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
• To evaluate the pharmacokinetics (PK) of amlitelimab and anti-drug antibodies to amlitelimab in participants with asthma	• Serum amlitelimab concentrations measured throughout the study • Incidence of anti-amlitelimab antibody positive response
• To evaluate the safety of amlitelimab in participants with asthma	• Percentage of participants with treatment-emergent adverse events (TEAEs), including local reactions, adverse events of special interest (AESIs), serious adverse events (SAEs) • Incidence of potentially clinically significant laboratory test, vital signs, and ECG abnormalities in the treatment period
• To evaluate the effects of amlitelimab on participant reported outcomes (PROs)	• Change from baseline in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered Score at Week 48 **(key secondary endpoint)** • AQLQ (S) Self-Administered Score at Weeks 2, 4, 8, 12, 24, 36, and 60 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Weeks 2, 4, 8, 12, 24, 36, 48, and 60 • Proportion of participants with a decrease from baseline of at least 4 points in SGRQ total score at Week 48
• To evaluate the effects of amlitelimab on ACQ-6 and ACQ-7	• Change from baseline in ACQ-6 score and ACQ-7 at Weeks 2, 4, 8, 12, 24, 36, 48, and 60
Tertiary/Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

1.2.1 Estimands

Primary estimand defined for primary and key secondary efficacy endpoints are summarized in below Table 2. More details are provided in Section 3.

Table 2 - Summary of primary estimand for the primary endpoint and key secondary efficacy endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To evaluate the efficacy of different doses of amlitelimab compared to placebo in participants with moderate-to-severe, uncontrolled asthma.				
Primary endpoint Primary estimand (treatment policy)	Annualized rate of severe exacerbation events over 48 weeks	ITT	**The following IEs may occur:** 1. Taking prohibited rescue medications or procedures post randomization. 2. Early discontinuation of study treatment due to lack of efficacy without taking prohibited rescue medication or procedure. 3. Early discontinuation of study treatment due to other reason without taking prohibited rescue medication or procedure. **The IEs will be handled as follows:** All three IEs above will be handled with **treatment policy strategy**. For participants who take rescue medication or procedure, or discontinue IMP due to any reason on or before Week 48, all severe asthma exacerbation events up to Week 48 will be included in the analysis irrespective of study treatment adherence or use of rescue medications and procedures; for participants who withdraw from the study prior to Week 48, the observation duration will be from randomization to Week 48 or to the last contact date, whichever is earlier.	• Estimated annualized event rate for each study intervention group and the corresponding 2-sided 95% confidence interval (CI). • The event risk ratio (RR) of each amlitelimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value. The annualized rate of severe asthma exacerbation will be analyzed using a negative binomial regression model. The model will include the total number of severe asthma exacerbation events that occur over 48 weeks as the response variable, with study intervention group, region (pooled country), screening eosinophil strata (<300 cells/μL or ≥300 cells/μL), number of asthma exacerbations in the previous 12 months strata (=1 or >1) and baseline ICS dose level (categorical variable) as covariates. Log-transformed observation duration will be the offset variable. **Missing data handling:** To account for a shorter duration of follow-up of participants with IEs prior to Week 48, the primary analysis negative binomial model will include an offset term for the logarithm of observation duration. No further imputation will be performed for the unobserved asthma events that may happen after study discontinuation and up to Week 48.
Secondary objective: To evaluate the effects of amlitelimab compared to placebo on lung function as measured by forced expiratory volume in 1 second (FEV1)				
Key secondary endpoint Primary Estimand (treatment policy)	Change from baseline in pre-bronchodilator (BD) FEV1 at Week 48	ITT	**The following IEs may occur:** 1. Taking prohibited rescue medications or procedures post randomization. 2. Early discontinuation of study treatment due to lack of efficacy without taking prohibited rescue	• Mean change from baseline in pre-BD FEV1 at Week 48 by study intervention group. • Difference in the least squares (LS) mean change from baseline in pre-BD FEV1 at Week 48 of each amlitelimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
			medication or procedure. 3. Early discontinuation of study treatment due to other reason without taking prohibited rescue medication or procedure. **The IEs will be handled as follows:** All three IEs above will be handled with **treatment policy strategy**. Participants who take rescue medication or procedure, or discontinue IMP due to any reason on or before Week 48 will be asked and encouraged to return to the clinic for all remaining study visits; their pre-BD FEV1 data at Week 48 will be included in the analysis irrespective of treatment adherence or use of prohibited medications and procedures.	The change from baseline in pre-BD FEV1 at Week 48 will be analyzed using ANCOVA model. The model will include change from baseline in pre-BD FEV1 value at Week 48 as response variable, and study intervention group, age, sex, height, region (pooled country), screening eosinophil strata (<300 cells/μL or ≥300 cells/μL), number of asthma exacerbations in the previous 12 months strata (=1 or >1), baseline ICS dose level (categorical variable) and the corresponding baseline value (continuous variable) as covariates. **Missing data handling**: Multiple imputation will be used to impute any missing values at the analysis timepoint (pre-BD FEV1 at Week 48). The multiple imputation will use all participants. Results from each complete dataset will be combined using Rubin's formula to provide the final efficacy results.
Secondary objective: To evaluate the effects of amlitelimab on Asthma Control Questionnaire 5 (ACQ-5)				
Key secondary endpoint Primary Estimand (treatment policy)	Change from baseline in ACQ-5 score at Week 48	ITT	The IEs, IEs handling are defined/described in the same way as those specified for the primary estimand for the key secondary endpoint of "Change from baseline in pre-BD FEV1 at Week 48".	• Mean change from baseline in ACQ-5 score at Week 48 by study intervention group. • Difference in the LS mean change from baseline in ACQ-5 score at Week 48 of each amlitelimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value. The key secondary endpoint of change from baseline in ACQ-5 at Week 48 will be analyzed using ANCOVA in the same fashion as for the primary estimand for the key secondary endpoint of "Change from baseline in pre-BD FEV1 at Week 48". The covariates to be included are study intervention group, age, region (pooled country), screening eosinophil strata (<300 cells/μL or ≥300 cells/μL), number of asthma exacerbations in the previous 12 months strata (=1 or >1), baseline ICS dose level (categorical variable) and the corresponding baseline value (continuous variable). **Missing data handling**: The same missing data handling method as for the key secondary endpoint/primary estimand of "Change from baseline in pre-BD FEV1 at week 48" will be used.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: To evaluate the effects of amlitelimab on participant reported outcomes (PROs)				
Key secondary endpoint Primary Estimand (treatment policy)	Change from baseline in Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered Score at Week 48	ITT	The IEs, IEs handling are defined/described in the same way as those specified for the primary estimand for the key secondary endpoint of "Change from baseline in pre-BD FEV1 at Week 48".	• Mean change from baseline in AQLQ (S) Self-Administered Score at Week 48 by study intervention group. • Difference in the LS mean change from baseline in AQLQ (S) Self-Administered Score at Week 48 of each amlitelimab regimen versus placebo, and the corresponding 2-sided 95% CI and p-value. The key secondary endpoint of change from baseline in AQLQ (S) Self-Administered Score at Week 48 will be analyzed using ANCOVA in the same fashion as for the primary estimand for the key secondary endpoint of "Change from baseline in pre-BD FEV1 at Week 48". The covariates to be included are study intervention group, age, region (pooled country), screening eosinophil strata (<300 cells/µL or ≥300 cells/µL), number of asthma exacerbations in the previous 12 months strata (=1 or >1), baseline ICS dose level (categorical variable) and the corresponding baseline value (continuous variable). **Missing data handling**: The same missing data handling method as for the key secondary endpoint/primary estimand of "Change from baseline in pre-BD FEV1 at week 48" will be used.

2 ANALYSIS POPULATIONS

[redacted]

Table 3 - [redacted]

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[redacted]

[redacted]

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

[redacted]

Table 4 - Selected prohibited rescue medication and procedures impact on efficacy

Medication	Action to IMP	Intervention in the main statistical analysis	Selection criteria
Anti-IL4R mAb (eg, dupilumab [Dupixent®])	IMP discontinuation	Yes	CDGsn00521
Anti-IL5 or IL-5R mAb (eg, benralizumab [Fasenra], mepolizumab [Nucala], or reslizumab [Cinqair])	IMP discontinuation	Yes	CDGsn00521
Anti-IgE mAb (eg, omalizumab [Xolair])	IMP discontinuation	Yes	CDG00486

Medication	Action to IMP	Intervention in the main statistical analysis	Selection criteria
Anti-TSLP mAb (eg, Tezepelumab [Tezspire®])	IMP discontinuation	Yes	CDGsn00521
Bronchial thermoplasty	IMP discontinuation	Yes	CMQ20097
Initiation of continuous oral corticosteroid treatment during the study beyond 14 days consecutively	IMP discontinuation	Yes	CDGsn00010 with route = 'oral' and treatment duration beyond 14 days consecutively

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

[redacted]

3.2.2 Main analytical approach

[redacted]

[redacted]

3.2.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.2.4 [redacted]

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[redacted]

[redacted]

3.3 SECONDARY ENDPOINT(S) ANALYSIS

[redacted]

3.3.1 Key/Confirmatory secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

[redacted]

[redacted]

[redacted]

3.3.1.2 Main analytical approach

[redacted]

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3.3.1.3 [redacted]

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3.3.2 Other secondary endpoint(s)

[redacted]

[redacted]

[redacted]

[redacted]

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

[redacted]

[redacted]

3.4.1 Definition of endpoint(s)

[redacted]

[redacted]

[redacted]

3.4.2 Main analytical approach

[redacted]

[redacted]

[redacted]

3.5 MULTIPLICITY ISSUES

[redacted]

Table 5 - [redacted]

[redacted]

3.6 SAFETY ANALYSES

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3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date +28 days, if the last IMP is prior to Week 24; and as last IMP administration date – first IMP administration date +84 days, if the last IMP is on or after Week 24, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- 0 and ≤ 8 weeks
- > 8 and ≤ 16 weeks
- > 16 and ≤ 24 weeks
- > 24 and ≤ 36 weeks
- > 36 and ≤ 48 weeks
- > 48 weeks

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

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3.6.2 Adverse events

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Table 6 - [redacted]

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Table 7 - [redacted]

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[redacted]

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Table 8 - [redacted]

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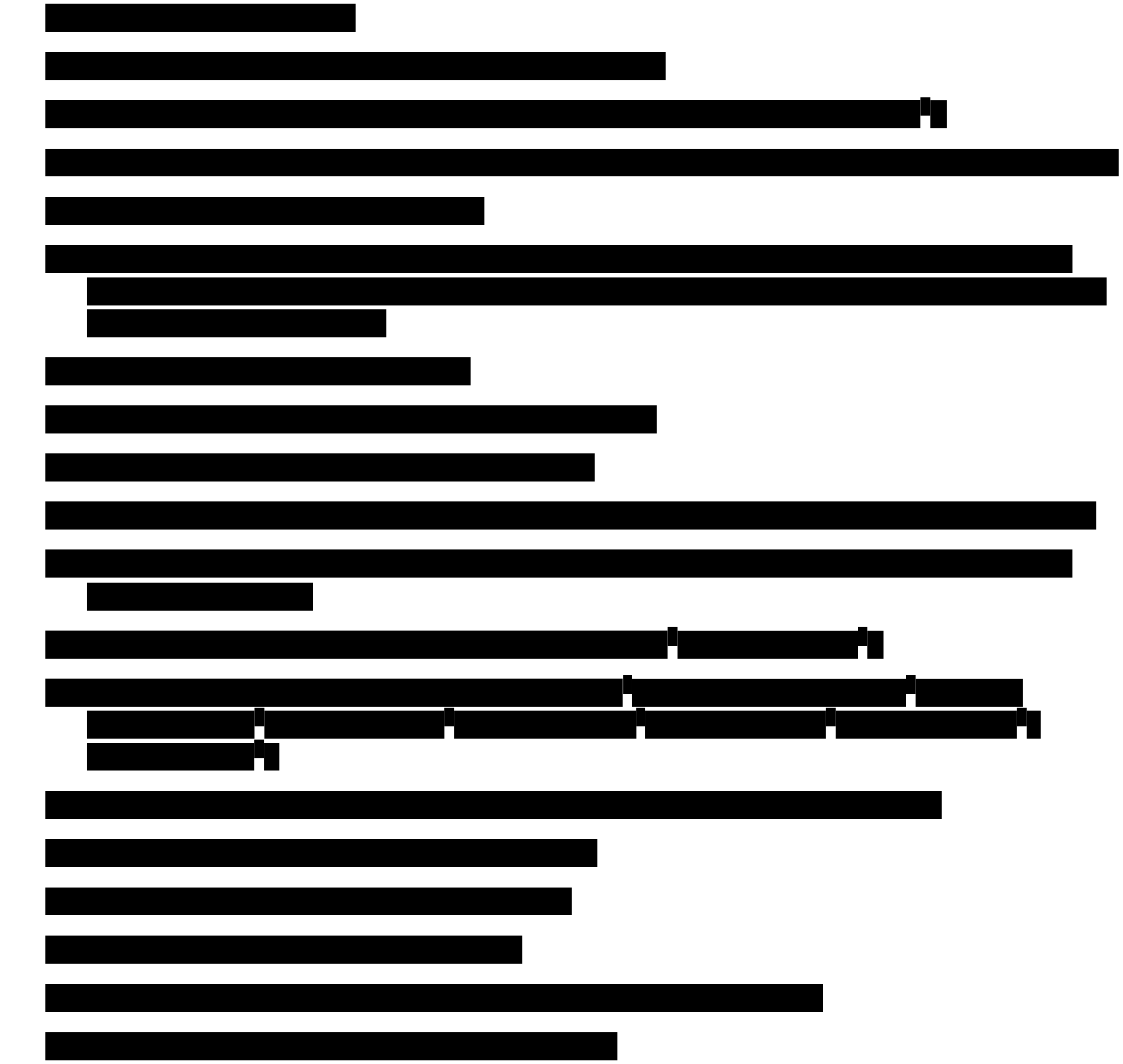
3.6.3 Additional safety assessments

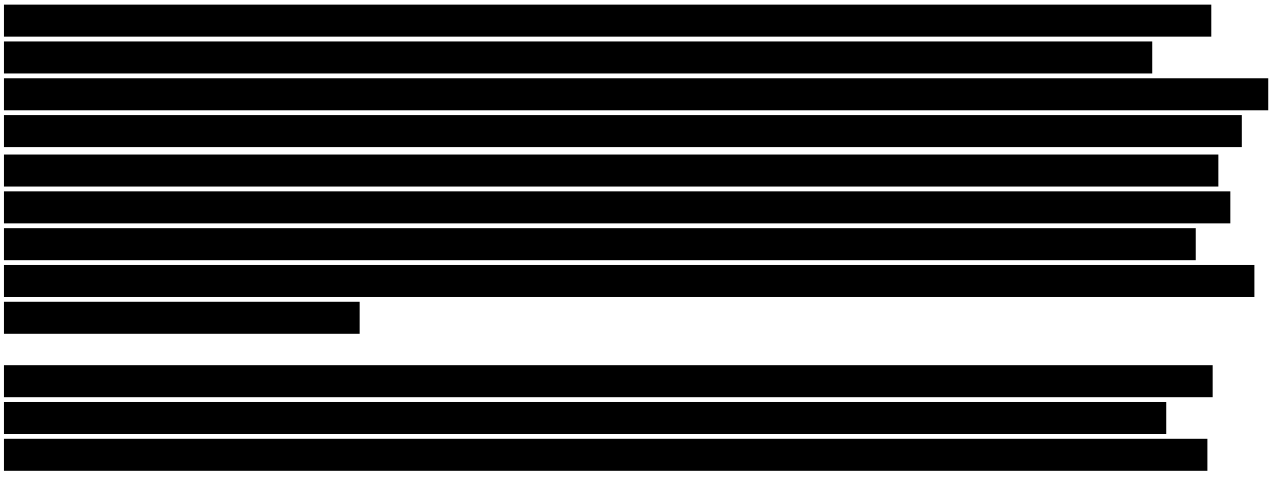
3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

[redacted]

3.6.4 [redacted]

[redacted]





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3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

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3.7.1.2 Immunogenicity analyses

[redacted]

[redacted]

3.7.1.3 Quality of life analyses

[redacted]

3.7.1.4 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.8 INTERIM ANALYSES

An interim analysis (IA) is planned to be performed when all randomized participants have completed at least 24 weeks of visit.

The purpose of the IA is to obtain early information for the planning of the Phase 3 program and to use the IA efficacy and safety data in health authority interaction. No alpha will be spent on the interim analysis as the analysis results will not make an early claim on the treatment effect of amlitelimab for efficacy endpoints and the study will continue unchanged irrespective of the interim analysis results. The full alpha will be spent on the primary analysis for this dose-finding study.

In order to maintain the further double-blinded conduct of the study, a separated unblinded team (IA team) will be setup to perform the IA. Any unblinded results or information will be strictly limited within the IA team, and any person being unblinded will no longer being involved in study operation and management to protect the study integrity. Participants, sites and study vendors, study operation and management team will remain blinded and will not have any access to the unblinded study folders or IA analysis results.

The *IA data cutoff date* is April 22nd, 2024, which is the date when all randomized subjects completed at least 24 weeks visit.

The **primary analysis population** for the interim analysis will be the ITT/randomized population. The analysis of the endpoints (provided below) will use all the data collected for this primary analysis population prior to the *IA data cutoff date*, including those who may have withdrawn from the study prior to Week 24.

There are two **secondary analysis populations** for the analyses of the primary endpoint:

1. **Week 48 analysis set**: it includes the participants who were randomized in the study early enough that the participant could have the opportunity to complete at least 48 weeks of treatment at the *IA data cutoff date*, including those who may have withdrawn from the study prior to Week 48.
2. **Week 60 analysis set**: it includes the participants who were randomized in the study early enough that the participant could have the opportunity to complete the entire 60-week

treatment period at the *IA data cutoff date*, including those who may have withdrawn from the study prior to Week 60.

The below parameters will be evaluated for the primary analysis population only:

- Participant disposition
- Demographics and baseline characteristics
- Medical history and comorbidities
- Prior & Concomitant Medications and procedures

The below parameters will be evaluated for the safety, PK/ADA or biomarker population only:

- The extent of exposure to investigational product and compliance
- Adverse events
- Laboratory values, ECG, vital signs
- PK/ADA

[redacted]

The below parameters will be evaluated for the primary analysis population, and the two secondary analysis populations, separately:

- Analysis of the annualized rate of adjudicated severe asthma exacerbations: The annualized event rate for each study intervention group, the ratio of the rates and relative rate reductions between each amlitelimab dosing regimen and placebo, and the corresponding 95% CI and p-values will be provided.
    - annualized rate of adjudicated severe asthma exacerbations prior to the *IA data cutoff date* up to Week 48 (primary analysis population)
    - annualized rate of adjudicated severe asthma exacerbations prior to Week 48 (Week 48 analysis set)
    - annualized rate of adjudicated severe asthma exacerbations prior during 60-weeks treatment period (Week 60 analysis set)
- Analysis of the change from baseline in pre-BD FEV1, ACQ-5 score and AQLQ(S): Descriptive statistics including number of patients, mean, standard error and LS mean for each treatment group will be obtained. Differences in the LS means, and 95% CIs and p-values of the differences will be provided for comparison between each amlitelimab dosing regimen and placebo will be provided.
    - Change from baseline pre-BD FEV1, ACQ-5 score and AQLQ(S) at Week 24 (primary analysis population)
    - Change from baseline in pre-BD FEV1, ACQ-5 score and AQLQ(S) at Week 48 (Week 48 analysis set)

- Change from baseline in pre-BD FEV1, ACQ-5 score and AQLQ(S) at Week 60 (Week 60 analysis set)

Other efficacy parameters, eg, including but not limited to post-BD FEV1, ACQ-6 score, FeNO, LOAC, etc. will also be analyzed on the primary analysis population.

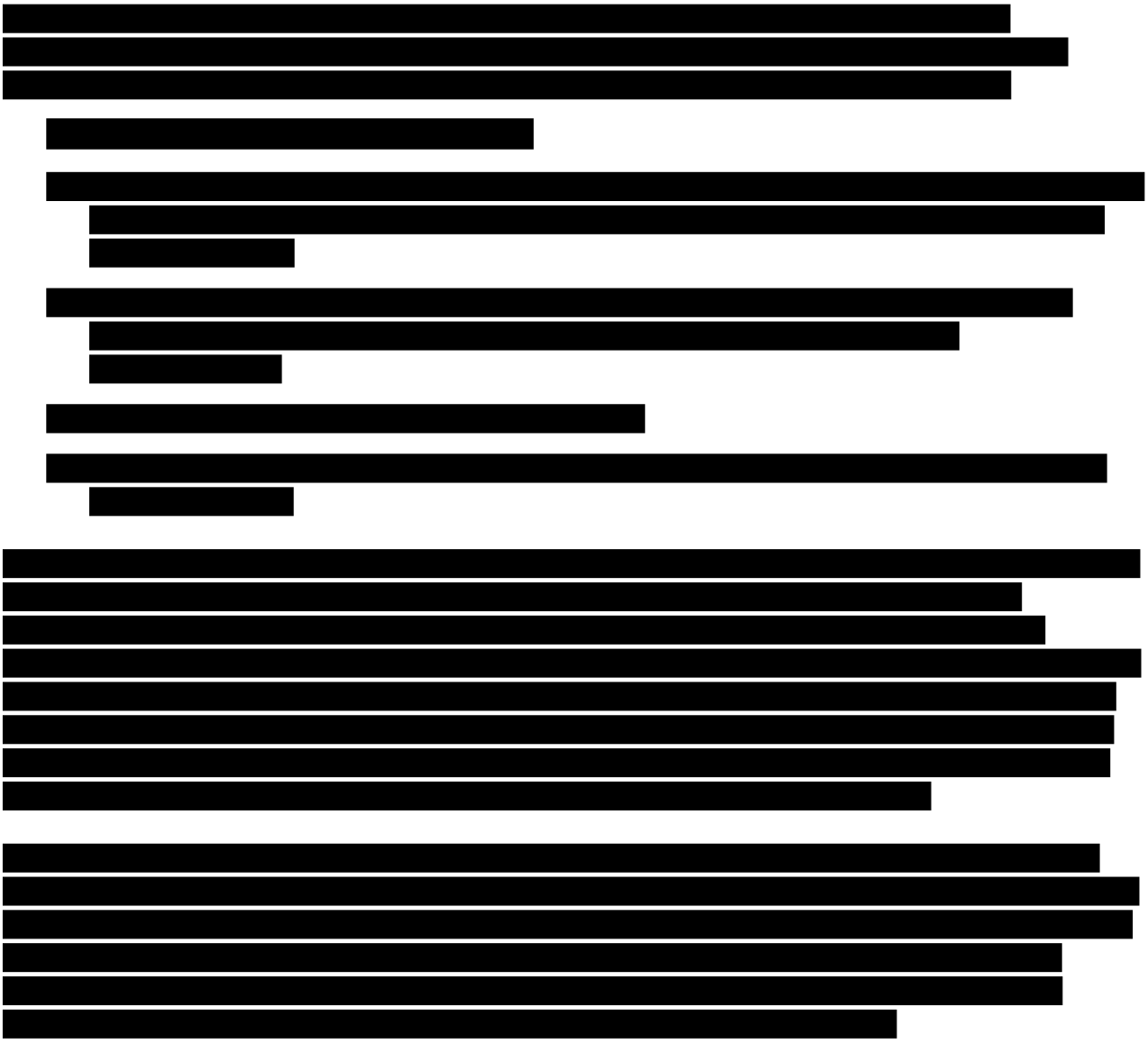
Analysis of the annualized rate of severe asthma exacerbations and the annualized rate of LOAC prior to the *IA data cutoff date* up to Week 48, and analysis of the change from baseline in pre-BD FEV1, ACQ-5, AQLQ(S), and FeNO at Week 24 will be performed on the primary analysis population by subgroups listed in Section 3.6.4.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at interim analysis:

- Participants without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Participants who did not complete treatment period nor prematurely discontinued the study intervention at cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their TE period, treatment period and concomitant medication period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last IMP date.
- Analyses of number of IMP administration and compliance will be performed up to the last IMP administration reported in the e-CRF up to the cut-off date.

AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an AE starting prior to the cut-off date will be taken into account. Medications, intervention discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.

4 SAMPLE SIZE DETERMINATION



5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ACQ: Asthma Control Questionnaire
ADA: anti-drug antibody
ADSD: asthma daytime symptom diary
AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
ANCOVA: analysis of covariance
ANSD: asthma nighttime symptom diary
AQLQ(S): Asthma Quality of Life Questionnaire with Standardized Activities
AST: aspartate aminotransferase
BD: bronchodilator
BMI: body mass index
CI: confidence interval
[redacted]
CSR: clinical study report
DNA: deoxyribonucleic acid
ECG: electrocardiogram
e-CRF: electronic case report form
eDiary: electronic diary
EOS: end of study
EOT: end of treatment
[redacted]
e-Spirometer: electronic spirometer
FDR: false discovery rate
FEF: forced expiratory flow
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 seconds
[redacted]
FVC: forced vital capacity
HGLT: high level group term
HLT: high level term
IA: interim analysis
ICF: informed consent form
ICS: inhaled corticosteroid
IE: intercurrent event
IFNγ: Interferon-gamma
Ig: immunoglobulin
IMP: investigational medicinal product

ISRs:	injection site reactions
ITT:	intent-to-treat
IVRS/IWRS:	Interactive Voice Response System/Interactive Web Response System
LABA:	long-acting beta agonist
LAMA:	long-acting muscarinic antagonist
LLT:	lower-level term
LOAC:	loss of asthma control
LS:	least squares
LTRA:	leukotriene receptor antagonists
LTS:	long term safety
MCF:	mean cumulation function
MCID:	minimal clinically important difference
MedDRA:	medical dictionary for regulatory activities
OCS:	oral corticosteroid
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PEF:	peak expiratory flow
[redacted]	
PK:	pharmacokinetic
PROs:	participant reported outcomes
PT:	preferred term
Q12W:	every 12 weeks
Q4W:	every 4 weeks
QoL:	quality of life
RBC:	red blood cell
RNA:	ribonucleic acid
RR:	risk ratio
SABA:	short-acting beta 2-agonists
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SD:	standard deviation
SGRQ:	St. George's Respiratory Questionnaire
SMQ:	standardized MedDRA query
[redacted]	
SOC:	system organ class
TARC:	Thymus and Activation-Regulated Chemokine
TB:	tuberculosis
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TSLP:	thymic stromal lymphopoietin
ULN:	upper limit of normal range
VAS:	Visual Analog Scale
WHO-DD:	World Health Organization-drug dictionary
WOCF:	worst-observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation
- Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19.

The number (%) of exposed and not randomized participants will also be summarized.

In addition, graphical summaries of the dropout patterns, such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if the missing data patterns are different between study intervention groups.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population as well as displayed separately as related versus not related to COVID-19 if applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (18 to <40, 40 to <65, 65 to 75)
- gender (Male, Female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Japanese, Not Reported, Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- region (Asia: Japan and South Korea; East Europe: Turkey, Hungary, Poland; Western Countries: United Kingdom, South Africa, Canada, USA, Italy; Latin America: Argentina, Brazil, Chile and Mexico)
- body weight group (<70, ≥70-<90, ≥90 kg)
- body mass index as quantitative variable and in categories (BMI, <25, ≥25-<30, ≥30-<35, ≥35 kg/m^2)
- smoking history (Never, Former)
- smoking quantity in pack-years for former smokers
- alcohol use will also be included in this summary as alcohol drinking frequency (Never, Occasional, At least daily, At least weekly, At least monthly) and number of standard alcohol drinks on a typical day when drinking (1 or 2, >2).

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

Allergic comorbidity medical history will be summarized separately, including:

- Comorbidities (Yes, Ongoing for each): Chronic spontaneous urticaria, Angioedema, Atopic dermatitis, Allergic rhinitis, Chronic sinusitis, Allergic conjunctivitis, Nasal polyposis, Food allergy and Eosinophilic esophagitis.

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by intervention group:

- Age at diagnosis of asthma (years)
- Time since diagnosis of asthma at randomization (years)
- Time since last asthma exacerbation at randomization (months)
- Number of asthma exacerbations experienced in the past 2 years before screening visit (quantitative variable and qualitative variable: 1, 2, 3, ≥4)

- Number of moderate asthma exacerbations experienced in the past 2 years before screening visit
- Number of asthma exacerbations experienced in the past 12 months before screening visit (quantitative variable and qualitative variable: 1, 2, 3, ≥4)
- Number of moderate asthma exacerbations experienced in the past 12 months before screening visit
- Randomization strata based number of severe asthma exacerbations experienced in the past year (=1, >1)
- Randomization strata based on screening eosinophil (<300 cells/mm3, ≥300 cells/mm^3)
- Baseline blood eosinophil level (<150 cells/mm^3, ≥150 to <300 cells/mm^3, ≥300 to <450 cells/mm^3, ≥450 cells/mm^3; <150 cells/mm^3, ≥150 cells/mm^3; <300 cells/mm^3, ≥300 cells/mm^3)
- Baseline pre-BD FEV1/FVC ratio (%), pre-BD FEV1 (L), pre-BD FVC (L), post-BD FEV1/FVC ratio (%), post-BD FEV1 (L), post-BD FVC (L), FEV1 reversibility (%), pre-BD FEV1 percent predicted (%), post-BD FEV1 percent predicted (%), pre-BD FVC percent predicted (%), and post-BD FVC percent predicted (%).
- Baseline ACQ-5, ACQ-6 and ACQ-7 score
- Baseline SGRQ total score
- Baseline AQLQ(S) score
- Baseline FeNO (quantitative variable and qualitative variable: (<25 ppb, ≥25-<50 ppb, ≥50 ppb; <25 ppb, ≥25 ppb)
- Asthma biologic treatment history (Yes, No)
- Background controller therapy (ICS-LABA, ICS-LABA-LAMA, ICS-LABA-LTR, other)
- Maintenance OCS (Yes/No); if yes, dose of OCS (low, medium, high)
- Background therapy containing ICS (Yes/No); if ICS were used, dose of ICS (quantitative variable and qualitative variable: low, medium, high.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.

- Concomitant medications are any medications received by the participant concomitantly to the IMP from the first administration of IMP to the last IMP intake + 168 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.

- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and ADA variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window. If there is no scheduled measurement within the visit window, the unscheduled measurement that is closest to the target date will be used (in case of tie select the latest).

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 9 - Analyses window definition for efficiency endpoints

Scheduled visit	Targeted study day	Time windows		
		Spirometry (pre-BD), ACQ-5, ACQ-6, ACQ-7, AQLQ(S), SGRQ	[redacted]	FeNO [redacted]
Visit 1 (W-5 to W-3)	-28 to -14			
Week 0 (Visit 2)	1	≤1		1
Week 2 (Visit 3)	15	2-21		2-21
Week 4 (Visit 4)	29	22-42		22-42
Week 8 (Visit 5)	57	43-70		43-70
Week 12 (Visit 6)	85	71-98		71-98
Week 16 (Visit 7)	113	99-126		99-140
Week 20 (Visit 8)	141	127-154		

Scheduled visit	Targeted study day	Time windows			
		Spirometry (pre-BD), ACQ-5, ACQ-6, ACQ-7, AQLQ(S), SGRQ	[redacted]	FeNO	[redacted]
Week 24 (Visit 9)	169	155-210		141-210	
Week 36 (Visit 10)	253	211-294		211-294	
Week 48 (Visit 11)	337	295-378		295-378	
Week 60 (Visit 12)	421	379-462		379-462	
Week 72 (Visit 13)	505	>462		>462	

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 10 - Analyses window definition for safety endpoints

Scheduled visit	Targeted study day	Time windows			
		Vital signs	Laboratory tests (include clinical chemistries)	12- lead EGC	Physical examination
Visit 1 (W-5 to W-3)	-28 to -14				
Week 0 (Visit 2)	1	≤1	≤1	≤1	≤1
Week 2 (Visit 3)	15	2-21			
Week 4 (Visit 4)	29	22-42	2-56		
Week 8 (Visit 5)	57	43-70			
Week 12 (Visit 6)	85	71-98	57-126		
Week 16 (Visit 7)	113	99-126			
Week 20 (Visit 8)	141	127-154			
Week 24 (Visit 9)	169	155-210	127-210		2-252
Week 36 (Visit 10)	253	211-294	211-294		
Week 48 (Visit 11)	337	295-378	295-378	2-378	253-378
Week 60 (Visit 12)	421	379-462	379-462	379-462	379-462
Week 72 (Visit 13)	505	>462	>462	>462	>462

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Table 11 - Analyses window definition for PK/PD and biomarker endpoints

		Time windows
Scheduled visit	**Targeted study day**	[redacted]
Visit 1 (W-5 to W-3)	-28 to -14	
Week 0 (Visit 2)	1	
Week 2 (Visit 3)	15	
Week 4 (Visit 4)	29	
Week 8 (Visit 5)	57	
Week 12 (Visit 6)	85	
Week 16 (Visit 7)	113	
Week 20 (Visit 8)	141	
Week 24 (Visit 9)	169	
Week 36 (Visit 10)	253	
Week 48 (Visit 11)	337	
Week 60 (Visit 12)	421	
Week 72 (Visit 13)	505	

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Calculation of numbers of inhalations/day of SABA or low-dose ICS/formoterol for symptom relief

The number of SABA or low-dose ICS/formoterol per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary. A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary Day 14 includes the evening dairy on Day 14 and the morning dairy on Day 15.

Starting from Day 8, for each time point Day X, periodical average of the number of inhalations/day of SABA or low-dose ICS/formoterol will be calculated as the mean number of SABA or low-dose ICS/formoterol per day from Diary Day X-7 to X-1. First IMP administration is used as the reference day (Day 1). For example, for Day 15, the periodical average window is from Dairy Day 8 to 14.

Periodical average of daily efficacy endpoints at designated study days

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day window. Starting from Day 8, for each time point Day X, periodical average for Morning FEV1, PEF and ANSD is from Day X-6 to X, and the periodical average for Evening FEV1, PEF and ADSD is from Day X-7 to X-1. First IMP administration is used as the reference day (Day 1).

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 ICS THERPY LEVEL

ICS doses would separate into three level: Low, medium, and high ICS doses in adults

1. GINA 2021.

Daily doses in this table are shown as metered doses. See product information for delivered doses.

Low, medium and high ICS doses: adults/adolescents

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; * see product information

2. Inhaled Corticosteroid in ICS/LABA combination

For Inclusion Criteria #3 and #4, the ICS doses for the ICS/LABA combinations were derived from GINA 2021 and using prescribing information.

Combination	Medium	High
Beclomethasone dipropionate (eg, Fostair®)	400	>400
Fluticasone propionate HFA (eg, Seretide®, Advair®)	500	>500
Fluticasone furoate (eg, Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (eg, Symbicort®)	640	>640
Mometasone Furoate (eg, Dulera®)	400	>400

5.6 APPENDIX 6 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI >2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

for Phase 2/3 studies

(From BTD-009536 – 21-MAY-2014)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20 bpm >100 bpm >100 bpm and increase from baseline ≥20 bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% >220 ms >220 ms and increase from baseline ≥25% >240 ms >240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

5.7 APPENDIX 7 ASTHMA CONTROL QUESTIONNAIRE (ACQ)

Asthma Control Questionnaire, 7-question version (ACQ-7)

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

For further information:

[redacted]

DECEMBER 2002

Revised September 2010
ACQ-SA North American English Version

ASTHMA CONTROL QUESTIONNAIRE©

PATIENT ID: _____

DATE: _____

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?

0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?

0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?

0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

Revised September 2010
ACQ-SA North American English Version

ASTHMA CONTROL QUESTIONNAIRE©

PATIENT ID: _____

DATE: _____

5.	In general, during the past week, how much of the time did you **wheeze?**	0 1 2 3 4 5 6	Not at all Hardly any of the time A little of the time A moderate amount of the time A lot of the time Most of the time All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 1 2 3 4 5 6	None 1 - 2 puffs/inhalations most days 3 - 4 puffs/inhalations most days 5 - 8 puffs/inhalations most days 9 - 12 puffs/inhalations most days 13 - 16 puffs/inhalations most days More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7.	FEV_1pre-bronchodilator: ..... FEV_1predicted: ..... FEV_1%predicted: ..... (Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	0 1 2 3 4 5 6	> 95% predicted 95 - 90% 89 - 80% 79 - 70% 69 - 60% 59 - 50% < 50% predicted

Revised September 2010
ACQ-SA North American English Version

5.8 APPENDIX 8 ASTHMA QUALITY OF LIFE QUESTIONNAIRE (AQLQ(S))

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

For further information:

[redacted]

Development and validation
supported by
GLAXO WELLCOME, INC

APRIL 2008

Modified September 2010
AQLQ(S)-SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*) *If you are not employed or self-employed, these should be tasks you have to do most days.	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Modified September 2010
AQLQ(S)-SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

Modified September 2010
AQLQ(S)-SA North American English Version

5.9 APPENDIX 9 ST GEORGE'S RESPIRATORY QUESTIONANAIRE FOR COPD PATIENTS (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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UK/ English (original) version 1

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:
- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one*:
- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

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St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

UK/ English (original) version 6

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5.10 APPENDIX 10 SGRQ SCORING ALGORITHM

A. Item Weights

PART 1

1. I have coughed:
   Most 80.6
   Several 63.2
   A few 29.3
   Only 28.1
   Not 0.0

2. I have brought up phlegm (sputum):
   Most 76.8
   Several 60.0
   A few 34.0
   Only 30.2
   Not 0.0

3. I have had shortness of breath:
   Most 87.2
   Several 71.4
   A few 43.7
   Only 35.7
   Not 0.0

4. I have had attacks of wheezing:
   Most 86.2
   Several 71.0
   A few 45.6
   Only 36.4
   Not 0.0

5. How many severe or very bad unpleasant attacks of chest trouble have you had?
   More than three 86.7
   3 attacks 73.5
   2 attacks 60.3
   1 attack 44.2
   None 0.0

6. How long did the worst attack of chest trouble last?
   a week or more 89.7
   3 or more days 73.5
   1 or 2 days 58.8
   less than a day 41.9

7. In an average week, how many good days (with little chest trouble) have you had?

None 93.3
1 or 2 76.6
3 or 4 61.5
nearly every day 15.4
every day 0.0

8. If you have a wheeze, is it worse in the morning?

No 0.0
Yes 62.0

PART 2

9. How would you describe your chest condition?

The most important problem I have 83 .2
Causes me quite a lot of problems 82.5
Causes me a few problems 34.6
Causes no problem 0.0

10. If you have ever had paid employment?

My chest trouble made me stop work 88.9
My chest trouble interferes with my work or made me change my work 77.6
My chest trouble does not affect my work 0.0

11. Questions about what activities usually make you feel breathless.

Sitting or lying still 90.6
Getting washed or dressed 82.8
Walking around the home 80.2
Walking outside on the level 81.4
Walking up a flight of stairs 76.1
Walking up hills 75.1
Playing sports or games 72.1

12. More questions about your cough and breathlessness.

My cough hurts 81.1
My cough makes me tired 79.1
I get breathless when I talk 84.5
I get breathless when I bend over 76.8
My cough or breathing disturbs my sleep 87.9
I get exhausted easily 84.0

13. Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public 74.1
My chest trouble is a nuisance to my family, friends or neighbours 79.1

I get afraid or panic when I cannot get my breath 87.7
I feel that I am not in control of my chest problem 90.1
I do not expect my chest to get any better 82.3
I have become frail or an invalid because of my chest 89.9
Exercise is not safe for me 75.7
Everything seems too much of an effort 84.5

14. Questions about your medication.

My medication does not help me very much 88.2
I get embarrassed using my medication in public 53.9
I have unpleasant side effects from my medication 81.1
My medication interferes with my life a lot 70.3

15. Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed 74.2
I cannot take a bath or shower, or I take a long time 81.0
I walk more slowly than other people, or I stop for rests 71.7
Jobs such as housework take a long time, or I have to stop for rests 70.6
If I walk up one flight of stairs, I have to go slowly or stop 71.6
If I hurry or walk fast, I have to stop or slow down 72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf 74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim 71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports 63.5

16. We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games 64.8
I cannot go out for entertainment or recreation 79.8
I cannot go out of the house to do the shopping 81.0
I cannot do housework 79.1
I cannot move far from my bed or chair 94.0

17. Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do 0.0
It stops me doing one or two things I would like to do 42.0
It stops me doing most of the things I would like to do 84.2
It stops me doing everything I would like to do 96.7

B. Outline of scoring algorithm

Three component scores are calculated: Symptoms; Activity; Impacts.

One Total score is also calculated.

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

i. The weights for all items with a positive response are summed.

ii. The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.

iii. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage :

Score = 100 x (Summed weights from positive items in that component/Sum of weights for all items in that component)

The Total score is calculated in similar way:

Score = 100 x (Summed weights from positive items in the questionnaire/Sum of weights for all items in the questionnaire)

Sum of maximum possible weights for each component and Total:

Symptoms 662.5

Activity 1209.1

Impacts 2117.8

Total 3989.4

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the participant).

The questionnaire requests a single response to questions 1-7, 9-10 and 17. If multiple responses are given to one of these questions, then averaging the weights for the positive responses for that question are acceptable.

Symptoms component: Calculated from the summed weights for the positive responses to questions 1-8.

Activity component: Calculated from the summed weights for the positive responses to questions 11 and 15.

Impacts component: Calculated from the summed weights for the positive responses to questions 9-10, 12- 14 and 16-17.

Total score: Calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire.

C. Handling of missed items if applicable

Symptoms: the symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the symptoms component (662.5) and from the total weight (3989.4).

Activity: the activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the activity component (1209.1) and from the total weight (3989.4).

Impacts: the impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the impacts component (2117.8) and from the total weight (3989.4).

5.11 APPENDIX 11 [redacted]

5.12 APPENDIX 12 [redacted]

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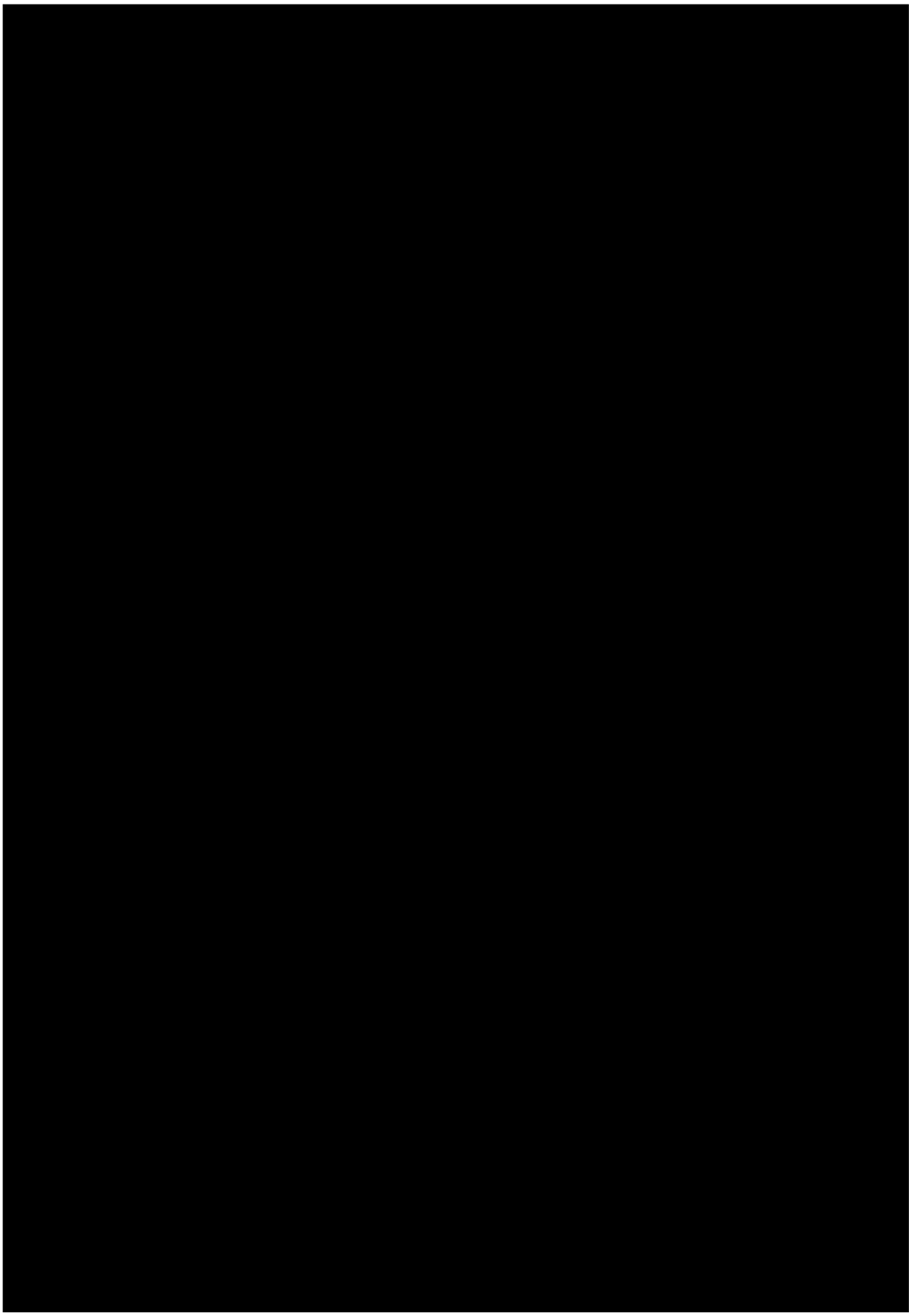

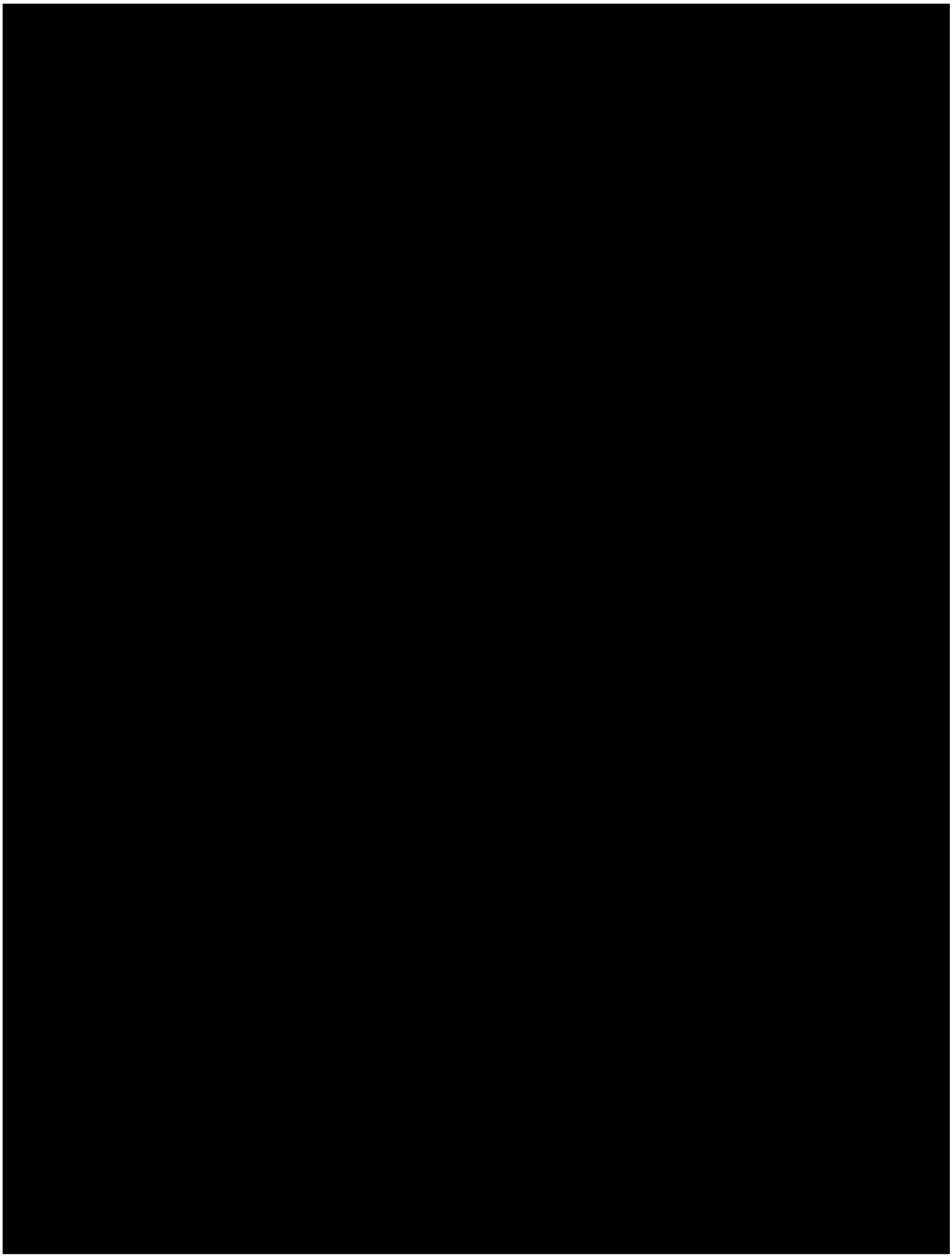

5.13 APPENDIX 13 [redacted]

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5.14 APPENDIX 14 LIST OF OPPORTUNISTIC INFECTIONS

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – only systemic or extensive mucosal or cutaneous candidiasis.
- Coccidioides immitis (endemic south-western US and Central and South America)
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Mycobacterium avium
- Nontuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)
- Tuberculosis (TB)

This list is indicative and not exhaustive.

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