Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Biomarker Study of the Effects of Dexpramipexole on Eosinophils in Subjects with Eosinophilic Asthma

[redacted]

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ACQ	Asthma Control Questionnaire
ADaM	analysis data model
AE	adverse event
AEC	absolute eosinophil count
[redacted]	[redacted]
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AQLQ	Asthma Quality of Life Questionnaire
AV	atrioventricular
CBC	complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
FeNO	exhaled nitric oxide
GINA	Global Initiative for Asthma
GEE	Generalized Estimating Equations
HR	heart rate
IA	interim analysis
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-effect model, repeated-measures
PCS	potentially clinically significant
PD	Protocol deviation
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate

QTcF	QT interval corrected for heart rate using Fridericia's formula
RIM	Risk and Issues Management
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SE	standard error
SI	International System of Units
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
WHODrug	World Health Organization Drug Dictionary

1. STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted]

Statistician

Sponsor approval:

[redacted]

Medical Monitor

[redacted]

Statistician

2. INTRODUCTION

This SAP has been developed after review of the clinical study protocol ([redacted] dated 16 July 2019) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK), efficacy and safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Knopp Biosciences LLC. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified and substantiated. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be approved by Knopp Biosciences LLC and detailed in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The SAP history is presented in Appendix 1.

3. STUDY OBJECTIVES

Primary Objective

The primary objective of this clinical trial is to evaluate the efficacy of dexpramipexole in reducing blood eosinophil count in subjects with eosinophilic asthma.

Secondary Objectives

The secondary objectives are as follows:

- To evaluate the safety and tolerability of dexpramipexole administered for 12 weeks in subjects with eosinophilic asthma
- To evaluate the efficacy of dexpramipexole on pulmonary function, asthma control, and quality of life
- To evaluate the relative effect of dexpramipexole 75 mg/day, 150 mg/day, and 300 mg/day on blood eosinophil count

Exploratory Objectives

The exploratory objectives are:

[redacted]

4. STUDY ENDPOINTS

Primary Endpoint

The primary endpoint of this study is the relative change in blood absolute eosinophil count from Baseline to Week 12.

Secondary Endpoints

Following are the secondary endpoints of the study:

- Change in pre-bronchodilator FEV1, from Baseline to Week 12
- Change in Asthma Control Questionnaire (ACQ-6) score, from Baseline to Week 12
- Change in post-bronchodilator FEV1, from Baseline to Week 12
- Change in quality of life, as measured by the Asthma Quality of Life Questionnaire (AQLQ), from Baseline to Week 12
- Incidence and severity of AEs, changes in vital signs, clinical laboratory safety tests, physical examination, body weight, and ECGs

Exploratory Endpoints

The following are the exploratory endpoints:

[redacted]

[redacted]

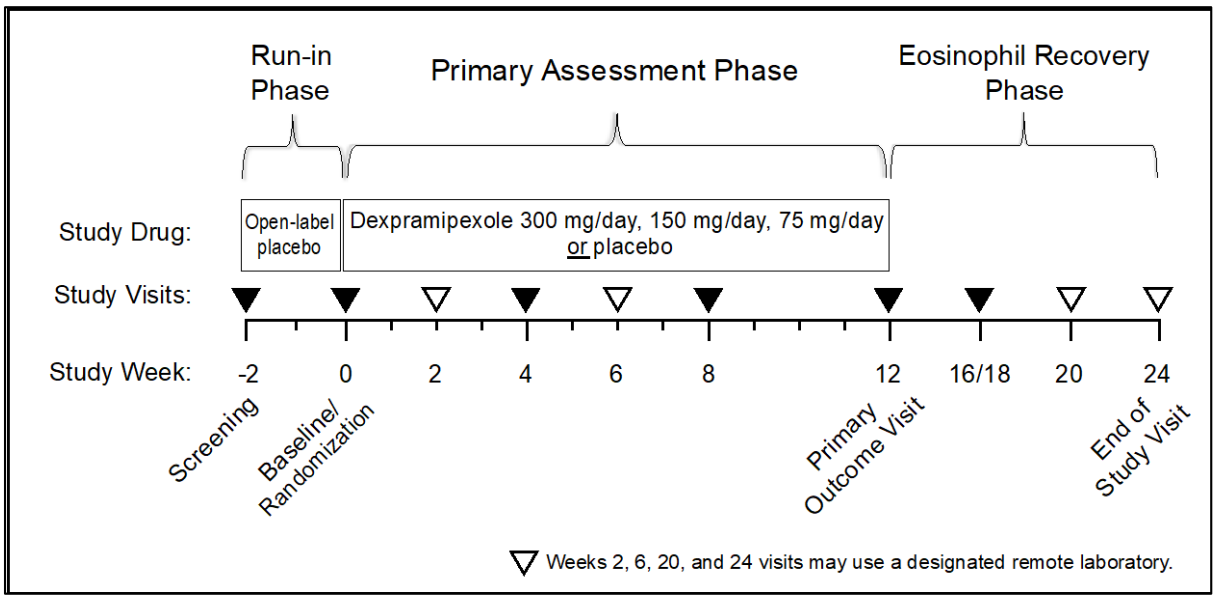
5. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multi-center study to evaluate the clinical effects of oral administration of dexpramipexole for 12 weeks on peripheral blood eosinophil count in subjects with eosinophilic asthma.

One hundred subjects will receive study drug (placebo, dexpramipexole 75 mg/day, 150 mg/day, or 300 mg/day randomly allocated in a 1:1:1:1 ratio) during the Primary Assessment Phase of the study (12 weeks of consecutive dosing). The study is expected to be conducted in approximately 25 centers [redacted]. After the Screening evaluations are completed, eligible subjects will enter a Run-in Phase of at least 12 days. Following the Run-in Phase, eligible subjects will enter the Primary Assessment Phase and receive twice-daily dosing of study drug for 12 weeks. During the Primary Assessment Phase, subjects will have study assessments performed at the site every 4 weeks, with additional safety and laboratory assessments at Week 2 and Week 6. Following Week 12, subjects will discontinue study drug and will begin a 12-week Eosinophil Recovery Phase, during which subjects will be monitored for recovery of eosinophil count. See Fig. 1 for details.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Schematic



6. SAMPLE SIZE JUSTIFICATION

The primary endpoint for this study is reduction in blood eosinophils from Baseline to Week 12. In an open label study of dexpramipexole in subjects with chronic rhinosinusitis with nasal polyps, dexpramipexole reduced eosinophils by 94% (ratio of endpoint to baseline = -2.81 on the log base e scale). The standard deviation for the ratio of endpoint to baseline was 1.82 on the log base e scale.

Nineteen subjects per arm will provide approximately 84% power if the true reduction in blood eosinophils is 85% with dexpramipexole and 10% with placebo. The power will be 95% if the true reduction in blood eosinophils is 90% with dexpramipexole and 10% with placebo. The sample size was calculated using methodology for a two-sample t-test. Assuming an approximate 20% dropout rate of subjects who do not have the final observation for blood eosinophils yields a sample size of 25 subjects per arm to be randomized.

7. STUDY TREATMENTS

The study treatment names and ordering to be used in the TFLs are presented in the table below.

Table 1: Presentation of Study Treatments in TFLs

Study Treatment	Order in TFLs
Placebo	1
75 mg/day dexpramipexole	2
150 mg/day dexpramipexole	3
300 mg/day dexpramipexole	4
Pooled 150 and 300 mg/day dexpramipexole	5

All treatments described above are the planned treatments, the pooled 150 and 300 mg/day dexpramipexole will be presented in selected outputs as indicated in the corresponding TFL shells document. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order.

8. DEFINITIONS OF ANALYSIS POPULATIONS

All protocol deviations identified, including those related to COVID-19, will be categorized prior to database lock. Each protocol deviation will be evaluated to determine if it might significantly affect the completeness, accuracy, and/or reliability of the study data or if it might significantly affect a subject's rights, safety, or well-being. Furthermore, important protocol deviations will be taken into consideration when assigning subjects to the analysis populations.

8.1. All Subjects Population

The all subjects population will include all subjects who signed the informed consent form (ICF) and had any study assessment recorded in the database per the protocol.

8.2. Safety Population

The safety population will include all subjects who were randomized and received at least one dose of study drug (placebo, dexpramipexole).

8.3. Efficacy Population

The efficacy population will be a modified intent-to-treat sample and consist of all subjects in the safety population who have at least one post-randomization evaluation for at least one of the efficacy endpoints (i.e., AEC, pulmonary function, asthma control, and quality of life).

Several subjects missed Pulmonary Function Tests due to COVID-19. For the analysis of pulmonary function tests the MMRM analysis will exclude subjects if they were missing both Week 8 and week 12 FEV1 due to COVID-19. Dexpramipexole is unlikely to show an effect on FEV1 at the week 4 visit and including only week 4 data may bias results against dexpramipexole. [redacted] Subjects who are missing spirometry due to other reasons will be included in the analysis.

For the analysis of ACQ-7 (which includes an FEV1 item) the MMRM analysis will exclude subjects if they were missing both Week 8 and week 12 FEV1 due to COVID-19.

Selected outputs as noted in the accompanying TFL shells document will be created for the subset of subjects in the efficacy population who were also hematological responders.

8.4. Recovery Phase Population

The Recovery Phase population consists of all subjects in the efficacy population who completed the Week 16/18 visit (started the Eosinophil Recovery Phase).

8.5. Per-protocol Population

The per-protocol population will include all subjects in the efficacy population who have an evaluable Week 8 or Week 12 AEC result while on study drug and had adherence ≥80% (based on number of tablets returned by subject compared to number expected to be taken during the period), and excludes subjects treated with systemic corticosteroids during the Primary Assessment Phase. Subjects that had a Baseline eosinophil count of $\leq 0.05 \times 10^9$/L at the Baseline visit lab draw will be excluded from the per protocol analysis, due to the lability of their eosinophil count prior to study drug.

Prior to the IA snapshot and release of treatment codes for the interim analysis, a final determination will also be made as to which subjects will be excluded from the per-protocol population. This definition may not be modified after the IA snapshot.

8.6. PK Population

The PK population will consist of all subjects in the safety population who have at least 1 quantifiable PK concentration.

9. STATISTICAL METHODOLOGY

9.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include all available data. Any subject who discontinued from the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, percentage changes from baseline, and any parameter derivations.

9.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum

Subjects who discontinue study drug prematurely will be asked to return within 4 days of the last dose of study drug for a premature discontinuation visit. Data will be assigned to the nearest scheduled visit, if the nearest scheduled visit is Week 12 then data will not be included in the Week 12 analyses if it occurred after Study Day 95.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 9.9.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

9.1.2. Triplicate Readings

For electrocardiogram (ECG) data only, where triplicate readings are intended to be taken, the mean of triplicate readings will be used in calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean based on the number of readings available will be used in calculations.

9.1.3. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the planned value(s) will be defined as an unscheduled value.

For lab data, unscheduled data will be attributed to the nearest visit and for the visit-wise summaries and statistical analyses the last non-missing result within a visit will be used for all visits apart from Week 12. If there was a valid result at the scheduled Week 12 visit then

that value will be used for the visit-wise summaries and statistical analyses, if there was not then the last non-missing result mapped to Week 12 will be used.

For non-lab data, unscheduled data will be attributed to the nearest visit and for the visit-wise summaries and statistical analyses the last non-missing result within a visit will be used. For occasions when a retest was performed, the data from the retest will be mapped to the appropriate visit and considered for inclusion in the analysis according to the rules specified in other sections of the SAP (i.e. for spirometry data after considering the rules detailed in section 9.2 and for other data using the last valid observation within a visit window).

Unscheduled data for a specific data type (PARAMCD) is only mapped to visits where that data type was scheduled to be taken by the protocol Schedule of Events. Unscheduled data will only be mapped to the last scheduled visit for a datatype if it is closer to that visit than to a subsequent visit where that procedure was not scheduled, otherwise it will be mapped to the nearest visit. Summaries and statistical analyses will only contain the specific protocol specified visits for each datatype.

For the analysis of outliers (shifts) and potentially clinically significant changes (labs, vital signs, and ECGs) all data will be used including unscheduled values.

9.1.4. Definitions of Baseline, Change from Baseline, and Percentage Change from Baseline

Baseline will be defined as the last valid value recorded prior to the first randomized dose of study drug, except for blood absolute eosinophil count, for which the Baseline value will consist of the geometric mean of all eosinophil counts obtained prior to the first randomized dose of study drug. If the date of the value is missing, it will be excluded from the Baseline calculation. If the time is incomplete/missing, and if it was an assessment scheduled to occur predose, it will still be considered as Baseline unless the incomplete date/time indicates the value was recorded after the first randomized dose of study drug. During the Recovery Phase data will be compared to Baseline values as detailed above.

Individual changes from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the timepoint. The mean change from Baseline will be defined as the mean of the individual changes from Baseline for all subjects.

Individual percentage changes from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the timepoint, then dividing this calculated value by the individual subject's Baseline value and multiplying by 100. The mean percentage change from Baseline will be defined as the mean of the individual percentage changes from Baseline for all subjects.

For Log transformed data geometric means and geometric means of the ratio of observed value to Baseline will be presented. The geometric mean ratio will be calculated by subtracting the log of the Baseline value from the log of the result at a specific visit, then taking the mean, then taking the antilog to get geometric mean ratio. The CI are calculated on the log scale and then back transformed by taking the antilog to get back to original scale.

See Section 9.1.3 for more detail on handling repeat and unscheduled readings in the calculations. See Section 9.1.2 for more detail on handling of triplicate readings in the calculations.

9.2. Spirometry

In accordance with professional guidelines available when study specifications were drafted, spirometry results were over-read by an independent vendor in accordance with *American Thoracic Society/European Respiratory Society (ATS/ERS) Standardization of Spirometry 2005 (Eur Respir J. 2005 Aug;26(2):319-38. doi: 10.1183/09031936.05.00034805*[3]).

For these statistical analyses, subsequently published professional guidelines for grading FEV1 and FVC were applied (*Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST*)[4]; see Figure 2. Screening, Baseline, and Week 12 with either an FEV1 or FVC grade of less than A were repeated, if possible (codified in RAPID memo C101104101-626, 2/17/2020) (where RAPID stands for Risk, Actions, Protocol Deviations, Issues and Decisions).

The [redacted] medical monitor will review the Vitalograph over-read and using the ATS/ERS grading system assign an FEV1 score to each spirometry session.

Figure 2: ATS Spirometry Grading System

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Table 10. Grading System for FEV_1 and FVC (Graded Separately)

Grade	Number of Measurements	Repeatability: Age >6 yr	Repeatability: Age ≤6 yr*
A	≥3 acceptable	Within 0.150 L	Within 0.100 L*
B	2 acceptable	Within 0.150 L	Within 0.100 L*
C	≥2 acceptable	Within 0.200 L	Within 0.150 L*
D	≥2 acceptable	Within 0.250 L	Within 0.200 L*
E	≥2 acceptable	>0.250 L	>0.200 L*
	OR 1 acceptable	N/A	N/A
U	0 acceptable AND ≥1 usable	N/A	N/A
F	0 acceptable and 0 usable	N/A	N/A

Definition of abbreviation: N/A = not applicable.
The repeatability grade is determined for the set of prebronchodilator maneuvers and the set of post-bronchodilator maneuvers separately. The repeatability criteria are applied to the differences between the two largest FVC values and the two largest FEV_1 values. Grade U indicates that only usable but not acceptable measurements were obtained. *Although some maneuvers may be acceptable or usable at grading levels lower than A, the overriding goal of the operator must be to always achieve the best possible testing quality for each patient.* Adapted from Reference 114.
*Or 10% of the highest value, whichever is greater; applies for age 6 years or younger only.

Within a given visit window, the following hierarchy will designate which spirometry results will be used for statistical analyses.

- Sessions with an "ACCEPTED" value in the SESSACC field.
- Sessions with an "A" value in the "FEV1GRADE" field (using FEV1 grading above)
- Sessions with an "B" value in the "FEV1GRADE" field (using FEV1 grading above)
- Sessions with an "C" value in the "FEV1GRADE" field (using FEV1 grading above)

Results from the above will be utilized according to the following data handling procedures and study visit windowing rules.

- If 2 sessions within a given visit window both have the same grade and that is the highest grade in the window, the latter session will be used in the analysis.
- The choice of which prebronchodilator and/or post-bronchodilator sessions will be used in the analysis will be independently based on selecting the highest graded session for each test type, and not necessarily a session that corresponds to the same date of the other test type.
- Any session with an FEV1 grade of D-F or U will be excluded from the analyses.
- All grading of Week 12 spirometry will be completed before the IA snapshot.

9.3. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the all randomized subjects population.

9.4. Screening Demographics and Baseline Characteristics

Demography, medical history and baseline disease characteristic data (duration of symptoms, severity of symptom scores, concomitant medication at baseline, etc.) will be summarized at study Baseline for the safety population and repeated for the efficacy and per-protocol populations.

Sex, race, and ethnicity will be summarized using counts and percentages. Age, height (cm), weight (kg), and body mass index (kg/m^2; calculated) will be summarized with descriptive statistics (number of subjects [n], mean, standard deviation [sd], median, minimum, and maximum). Age will also be summarized according to the categories of less than 50 years, 50 to 65 years, and more than 65 years, using counts and percentages.

9.5. Study Drug Details

Randomization details will be listed. Details of randomized study drug allocation and administration will be listed along with adherence. Descriptive statistics will be provided for duration of dosing (days) and mean daily dose (mg) of study drug by treatment. The frequencies of duration of exposure will also be provided in monthly intervals.

A frequency table by treatment will be provided for study drug adherence according to the following categories:

- <60%
- ≥60% and <80%
- ≥80% and <120%
- ≥120%
- >90% and <105%

Descriptive statistics of the percentage adherence will also be provided by treatment.

9.6. Prior and Concomitant Medication

Medications classified as present at baseline are all medications taken prior to the date of first dose of randomized study drug which are either ongoing or with a stop date after the first day of randomized dosing. Concomitant medications include all medications present at baseline and all medications with a start date on or after the date of first dose of randomized study medication and prior to or on the date of last dose of randomized study medication. For inclusion in the summary of concomitant medications during the Primary Assessment Phase, the medication start date must be on or before the date of completion or date of discontinuation of the Primary Assessment Phase. Medications with a start date on or after the start date of the Recovery Phase will not be included in the summary of concomitant medications for the Primary Assessment Phase.

If the end date/time of a medication is incomplete or missing it will be assumed to be concomitant unless the incomplete end date/time indicates the medication finished prior to the first dose of randomized study drug or the start date indicates it started in the Recovery Phase.

Baseline and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2019 (or later if upversioned during the study). Baseline and concomitant medications will be summarized by ATC Class, Preferred Term and treatment and listed. For the summaries subjects will only be counted once per ATC Class and Preferred Term. All baseline and concomitant medication will be listed. A separate listing will also be provided for subjects that changed ICS/LABA Inhaler Medication during the study (either the type of the medication or the dose).

9.7. Pharmacokinetic/Efficacy Assessments

Dexpramipexole concentrations in plasma will be summarized using means, SD, standard error of the mean, coefficient of variation, minimum, median, and maximum by treatment per visit. The mean of the trough concentrations at Weeks 4, 8 and 12 will be calculated for each individual subject and will also be summarized by treatment. A scatterplot of dexpramipexole trough concentrations (mean of the 3 trough samples) in plasma will be used to evaluate the relationship between dexpramipexole exposure and eosinophil-lowering response at Week 12. Additional analyses may also be performed following review of the study data.

A scatterplot of dexpramipexole concentrations in plasma versus change from baseline in heart rate (ΔHR) and QTc interval (ΔQTcF) will also be created for Week 8, predose and 2 h 12-lead values versus observed dexpramipexole concentrations at the same time points.

9.8. Efficacy Assessments

9.8.1. General Methods of Analysis

The study will use a blocked randomization stratified by study site. Due to the large number of study sites and the expected small number of subjects at each site, the data from all sites will be pooled. Site will not be included in any of the statistical analysis models. The safety population will be used for all safety analyses and the efficacy population will be used for

efficacy analyses. Descriptive statistics, including means, medians, and standard error will be presented for efficacy measures for observed values and changes from baseline by scheduled evaluation time and treatment group. If the endpoint is one that requires a log transformation, then descriptive statistics will be geometric means and ratios. If the endpoint is one that requires a rank transformation, then descriptive statistics will be median and intra-quartile values.

To control the alpha level for testing three dose groups versus placebo for the primary endpoint and for testing FEV1, a closed hierarchical testing procedure will be used in the following order:

1) First, the 300mg/day dose group will be tested versus placebo for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
2) the 150 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
3) the pooled 150 and 300 mg/day dose groups will be tested versus placebo at the 0.05 level for change in pre-bronchodilator FEV1 at Week 12 then,
4) the 75 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level.

Statistical testing for the other secondary study endpoints will be performed at the 0.05 level without adjustment.

The primary endpoint and the secondary endpoints will also be analyzed using the per-protocol population.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to half of x, whereas >x and ≥x values will be set to x.

9.8.2. Interim Analysis (IA) of the Primary Assessment Phase

There will be an interim analysis of efficacy after the final subject has completed the Primary Outcome Visit (Week 12). The interim analysis will include the analyses of the primary and secondary efficacy endpoints through the Primary Outcome Visit (Week 12), but will also include a review of all available safety and clinical laboratory data, including all available data collected from subjects visits beyond Week 12.

An unblinded statistics and programming team will be assembled to perform the interim analysis. The primary statistics and programming study team will retain responsibility for performing the final study analyses and will not have access to the IA results and will remain blinded until the final database lock.

The data management, clinical and medical teams responsible for cleaning and performing the IA snapshot of the data for the interim analysis will not have access to the IA results and

will not have access to treatment assignments following the interim analysis. However, the sponsor [redacted] will have access to the unblinded results and the treatment codes following the IA snapshot for the interim analysis.

At the time of the interim analysis, it is expected that 100% of subjects will have completed the study through the Primary Outcome Visit (Week 12). Furthermore, approximately 50% of subjects will also have completed the study through the end of the Eosinophil Recovery Phase (Week 24). The remaining active subjects at the time of the interim analysis will be active in the Eosinophil Recovery Phase between Week 12 and Week 24 visits.

Prior to the release of unblinded treatment codes for the interim analysis, all available data in the study database will be cleaned and there will be a formal snapshot of the database. This includes collection and cleaning of all data from all subject visits completed prior to the final subject randomized completing the Primary Outcome Visit (Week 12).

Prior to the IA snapshot and release of treatment codes for the interim analysis, a final determination will also be made as to which subjects will be excluded from the per-protocol population. This definition may not be modified after the IA snapshot.

There will be no adjustment of p-values for the interim analysis because all subjects will have completed the Primary Assessment Phase and the results of the final analysis of efficacy through the Primary Assessment Phase should be identical to the results of the interim analysis of efficacy through the Primary Assessment Phase. Any changes to the efficacy results between the interim analysis of efficacy through Week 12 and the final analysis of efficacy through Week 12 will be noted, although none is expected.

At the same time an analysis of available safety data will be completed: Incidence of AEs and AEs leading to discontinuation of study drug; potentially clinically significant changes in vital signs, neutrophils; LFTs, and ECGs. This includes data from all subject all visits populated in the study database at the time of the interim analysis,

Safety data from this analysis may be updated for the final analysis, for instance, if an AE that was ongoing at Week 12 resolves by the end of the Eosinophil Recovery Phase (final database lock). After all subjects complete the End of Study Visit (Week 24), the study database will be locked, and the final analysis will be completed see below sections.

9.8.3. Primary Endpoint Analyses

The primary endpoint of this study is the change in blood absolute eosinophil count from Baseline to Week 12. Absolute eosinophil count will be transformed to the log10 scale. To avoid taking the log of zero, zero values (not null values) will be replaced with 5/μL in conventional units or 0.005×10^9/L in the International System of Units (SI), which is 50% of the lower limit of quantification. The geometric mean of all eosinophil counts obtained between the Screening and Baseline visits will be used to establish the baseline eosinophil count used in the efficacy analyses. Geometric means and standard errors will be presented by treatment group for observed values ratio to baseline at each visit along with a p-value comparing each dexpramipexole treatment group to placebo (ratio to baseline) based on an analysis of variance (ANOVA).

The primary analysis will be a mixed-effect model, repeated-measures (MMRM). The response variable will be the log transformed post-baseline value minus the log transformed baseline value. The model will include terms for log transformed baseline, Global Initiative for Asthma (GINA) treatment steps 3-5 as a categorical variable, treatment as a categorical variable, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subject as a random effect. An unstructured covariance will be used. Dexpramipexole dose group treatment effects and treatment group effects versus placebo at Week 12 will be tested by contrasts within the MMRM. Estimated LS means of treatment effects and estimated difference in treatment effects at each visit will be back transformed to the original scale to present estimated geometric means for treatment effects and ratio of geometric means of treatment effects versus placebo along with 95% CI.

A contrast will be created to test the treatment effect at Week 12 for the pooled 150 mg/day and 300 mg/day group versus the placebo group.

[redacted]

[redacted]

Two sensitivity analyses will be performed.

- An analysis of covariance (ANCOVA) model adjusting for baseline and the 3 levels of GINA treatment step as a categorical variable. Missing data will be replaced using multiple imputation. The Markov chain Monte Carlo method will be used, and prediction variables will be baseline eosinophil count, eosinophil count at visits prior to the missing data, and the 3 levels of GINA treatment step as a categorical variable. SAS PROC MI will be used to generate multiple complete datasets. To ensure robustness of results, 10 complete datasets will be created. Each of the 10 complete data sets will be separately analyzed as in the ANCOVA described above, and the results synthesized by SAS procedure MIAnalyze. The seed for the simulation will be 85246563.
- Dexpramipexole dose group treatment effects versus placebo at Week 12 will be tested on the original (non-log10 transformed) scale (ratio of Week 12 value to baseline value) using a Wilcoxon/Mann-Whitney rank sum test with last observation carried forward to replace missing Week 12 observations.

9.8.4. Secondary Endpoint and Exploratory Endpoint Analyses

Frequency tables with the number and percentage of subjects with a reduction from baseline in eosinophils <50%, 50% to <75%,75% to <90% and ≥ 90% will be presented by treatment and timepoint (up to Week 12). A hematologic responder is defined as a subject with a Week 12 blood eosinophil count of $\leq 0.05 \times 10^9$/L ($\leq$50 cells/μL). At each visit, the proportion of subjects with an AEC of $\leq 0.05 \times 10^9$/L ($\leq$50 cells/μL) will be compared between each active dose and placebo using a Fisher's exact test for the observed data. At each visit, the proportion of subjects with a ≥ 90% reduction of AEC relative to Baseline will be compared between each active dose and placebo using a Fisher's exact test for the observed data.

A Generalized Estimating Equations (GEE) model will be used to analyze the proportion of subjects with an AEC of $\leq 0.05 \times 10^9$/L over time to obtain an estimate of the treatment effect and p-value at Week 12. Parameters will be included for treatment, time and the treatment by time interaction and GINA as a covariate. A similar analysis will be performed for the proportion of subjects with a $\geq$ 90% reduction of AEC.

The number and percentage of subjects with eosinophil count rebound (defined as an eosinophil count of $>1.00 \times 10^9$/L (1000 cells/µL) and >200% of the baseline value during the Eosinophil Recovery Phase) will be presented by treatment and timepoint.

Geometric mean (standard error) profiles for eosinophil counts and ratios to baseline will be plotted.

Eosinophil count recovery (hematologic responders only) will be summarized in a frequency table with the number and percentage of subjects who have Eosinophil Count ≥50% of Baseline and will be presented from Week 12 to Week 24.

The ratio to baseline in eosinophil counts will be plotted versus days since last dose of randomized study drug for the Recovery Phase population (hematologic responders only) including a lowess regression line.

A scatterplot of change from baseline in FEV1 (y-axis) will be plotted versus the ratio to baseline in eosinophil count (x-axis log10 scale). A regression line and appropriate correlation coefficient will be added to the figure if appropriate.

Data for the following endpoints including changes from baseline will be summarized using descriptive statistics by treatment and timepoint:

- Pre and post-bronchodilator Spirometry data (including reversibility)
- ACQ-7 and ACQ-6
- AQLQ
- Basophils
- Eosinophil Progenitors
- Nasal Eosinophil Peroxidase
- Pharyngeal Eosinophil Peroxidase
- Exhaled Nitric Oxide Test (FeNO)

During the COVID-19 pandemic, pulmonary function testing was temporarily suspended, therefore there will be missing data for FEV1, which also contributes to question 7 of the ACQ-7. To minimize the amount of lost data the ACQ-6 will be used as the primary assessment of asthma symptoms.

For ACQ-7, if the 7th item has a missing score then the corresponding total score will be set to missing.

For MMRM analysis of FEV1 the analysis will be performed excluding all results from subjects missing both Week 8 and week 12 FEV1 due to COVID-19 exigencies. Due to its known pharmacodynamics, dexpramipexole is unlikely to show an effect on FEV1 at the week 4 visit and including only week 4 data may lead to misleading bias against demonstrating treatment effect; that, the exclusion should not introduce and should eliminate bias. Subjects who are missing FEV1 results due to other reasons will be included in the analysis. An analysis of all subjects in the efficacy population will also be performed. Additionally, an exploratory analysis of spirometry data using the MMRM analysis will be performed including Week 16/18 data in the place of missing Week 12 data, for those subjects missing both Week 8 and Week 12 spirometry.

For MMRM analysis of ACQ-7 the analysis will also be performed excluding subjects missing both Week 8 and week 12 FEV1 due to COVID-19. An analysis of all subjects in the efficacy population will also be performed.

At each visit the proportion of subjects with a ≥12% increase in FEV1 relative to Baseline will be compared between each active dose (as well as the pooled 150 and 300 mg/day dose groups) vs. placebo using a Fisher's exact test.

A GEE model will be used to analyse the proportion of subjects with a ≥12% increase in FEV1 relative to Baseline over time to obtain an estimate of the treatment effect and p-value at Week 12. Parameters will be included for treatment, time and the treatment by time interaction and GINA as a covariate. Subjects missing both Week 8 and week 12 FEV1 due to COVID-19 will excluded from the analysis.

For continuous endpoints measured more than once on treatment, the analysis will use the method used for the analysis of the primary endpoint, MMRM. The model will contain terms for Baseline, the 3 levels of GINA treatment step as a categorical variable, treatment, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subject as a random effect to compare treatment group effects.

For continuous endpoints measured only at Baseline and Week 12 the analysis will use ANCOVA, adjusting for the Baseline value and the 3 levels of GINA treatment step as a categorical variable. If a subject has a missing score at Week 12 and an evaluation was performed at the time of drop out, last observation carried forward (LOCF) will be used to impute the missing value at Week 12.

During the analyses residual plots will be assessed to determine if log or rank transformations are required. Linear dose response with dose on the log10 scale will be assessed rather than log linear if the dependent variable is not log transformed for the analysis. For this analysis a value of 1 will be added to all the dose levels to allow for the log10 transformation of the placebo dose.

For FEV1 Reversibility (%) is calculated as:

[FEV1 (post-bronchodilator) – FEV1 (pre-bronchodilator)] x 100)/ FEV1 (pre-bronchodilator)

and Reversibility (mL) is calculated as:

FEV1 (post-bronchodilator) – FEV1 (pre-bronchodilator).

Frequency tables with the number and percentage of subjects that have a change from baseline in ACQ-6 Total Scores at Week 12 of ≥0, <0 to to-0.5, -0.5 to -1.0 and <-1.0 will also be presented. The proportion of subjects with a change from baseline in ACQ-6 score ≤-0.5 will be compared between each active dose and placebo at Week 12 using a Fisher's exact test.

A GEE model will be used to analyze the proportion of change from baseline in ACQ-6 score ≤-0.5 over time to obtain an estimate of the treatment effect and p-value at Week 12. Parameters will be included for treatment, time and the treatment by time interaction and GINA as a covariate.

9.9. Safety and Tolerability Assessments

9.9.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or higher if upversioned during the study).

- A placebo run in adverse event will be defined as an AE that starts during the placebo run in phase or a pre-existing condition that increases in severity during the placebo run in. Placebo run in adverse events will be summarized by System organ class, preferred term, and treatment.
- An Eosinophil Recovery Phase adverse event will be defined as an AE that starts during the Eosinophil Recovery phase or an AE that increases in severity during the Eosinophil Recovery Phase. Eosinophil Recovery Phase adverse events will be summarized by System organ class, preferred term, and treatment.

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the first dose of randomized study drug and within 30 days of the last dose of study drug, or starts prior to the first dose of randomized study drug and increases in severity after the first dose of randomized study drug.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly, probably, or definitely related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the first randomized dose for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment

- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment
- System organ class, preferred term, week of onset from first dose of randomized study drug, and treatment for the system organ class of infections and infestations only.

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the first dose.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the first randomized dose is 01MAY2019/08:00 and recorded start date/time of an adverse event is 03MAY2019, then the minimum possible onset time will be calculated by assuming the adverse event started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).
- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an adverse event date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the adverse event ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).
- For the calculation of summary statistics: AEs for which the severity is missing will not have the severity imputed so for summaries by severity are counted only in the overall total
- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded or the maximum relatedness category.

- AEs will only be counted once per system organ class and once per preferred term. For the summary of AEs by severity, if a subject has multiple events occurring in the same body system or same preferred term, then the event with the highest severity will be counted. The relationship to study treatment will be classified as related or not related.

9.9.2. Hematology Parameters, including Neutrophil Count

Descriptive statistics for all raw values as well as change from baseline for each test will be presented for each visit and treatment group.

[redacted] To better characterize any episodes of neutropenia that may occur, a neutropenia case report form will be utilized to capture detailed clinical information concurrent with any laboratory-defined events of neutropenia. The responses to the questions from the neutropenia assessment case report form (CRF) (Yes/No answers only) will be summarized in a frequency table by treatment and whether temporarily related to neutropenia or control. The summary will include the number of subjects with each specific symptom and the number of occurrences of each specific symptom.

For the analysis of neutropenia, there will be tabulation of nadir ANC according to the following categories from Day 1 to Week 12 and also from Day 1 to Week 24:

- $<1.50 \times 10^9$/L
- 1.50×10^9/L to 1.99×10^9/L
- 1.00×10^9/L to 1.49×10^9/L
- 0.50×10^9/L to 0.99×10^9/L
- $<0.50 \times 10^9$/L

The incidence of infection AEs temporally related to neutropenia for dexpramipexole and placebo subjects will be compared using frequency tables. Temporal relationship is defined as an infection AE starting +/- 10 days of a neutropenic laboratory result.

9.9.3. Clinical Laboratory Parameters

For hematology and blood chemistry, descriptive statistics for raw values as well as change from baseline for each test will be presented for each visit and treatment along with shift tables. Boxplots will be presented for eosinophils only. For hematology, blood chemistry and urinalysis, the number and percentage of subjects with potentially clinically significant (PCS) laboratory results will be tabulated according to the criteria below:

The tabulation of PCS laboratory results will use all the data up to the last visit of the Primary Assessment Phase including unscheduled visits and will also be repeated including the washout visits.

Table 2: List of Potentially Clinically Significant Laboratory Findings

Hematology		
Test	**Low**	**High**
White blood cells (WBC)	< 3.0 x 10^9/L	≥ 16 x 10^9/L
Neutrophils	< 1.5 x 10^9/L	≥13.5 x 10^9/L
Lymphocytes	< 0.8 x 10^9/L	> 12 x 10^9/L
Monocytes	N/A	> 2.5 x 10^9/L
Eosinophils	N/A	> 1.6 x 10^9/L
Basophils	N/A	> 1.6 x 10^9/L
Hemoglobin - Females	≤ 9.5 g/dL	≥ 17.5 g/dL
Hemoglobin - Males	≤ 11.5 g/dL	≥ 19.0 g/dL
Hematocrit - Females	≤ 32%	≥ 54%
Hematocrit - Males	≤ 37%	≥ 60%
Red blood cells (RBC)	≤ 3.5 x 10^9/L	≥ 6.4 x 10^9/L
Platelet count	≤ 75 x 10^9/L	≥700 x 10^9/L
Biochemistry		
Test	**Low**	**High**
Sodium	≤ 126 mmol/L	≥156 mmol/L
Potassium	≤ 3 mmol/L	≥ 6 mmol/L
Chloride	≤ 90 mmol/L	≥118 mmol/L
Bicarbonate	≤ 16 mmol/L	≥ 35 mmol/L
Calcium	≤ 2 mmol/L	≥ 3 mmol/L
Magnesium	≤ 0.5 mmol/L	≥1.2 mmol/L
Inorganic phosphorus	≤ 0.6 mmol/L	≥1.7 mmol/L
Aspartate aminotransferase (AST)	N/A	≥ 3 x ULN
Alanine aminotransferase (ALT)	N/A	≥ 3 x ULN
Alkaline phosphatase	N/A	≥ 1.5 x ULN
Creatinine - Females	N/A	≥176.8 umol/L
Creatinine - Males	N/A	≥176.8 umol/L
Blood urea nitrogen (BUN)	N/A	≥10.7 mmol/L
Total bilirubin	N/A	≥ 1.5 x ULN
Total protein	≤ 45 g/L	≥ 100 g/L
Albumin	≤ 25 g/L	N/A
Uric acid - Females	N/A	≥ 506 umol/L
Uric acid - Males	N/A	≥ 625 umol/L
Glucose	≤2.2 mmol/L	≥ 9.7 mmol/L
Hy's Criteria Bilirubin ≥2 and (AST or ALT ≥ 3xULN)		
Urinalysis		
Test	**Low**	**High**
Protein	N/A	≥ ++
Ketones	N/A	≥ ++++
Glucose	N/A	++++

Note: Defined PCS laboratory criteria.
Note(s): N/A = not applicable; PCS = potentially clinically significant, ULN = upper limit of normal;

Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). PCS laboratory values will also be flagged in the listings.

9.9.4. Vital Signs Parameters

Vital sign measurements as well as change from baseline will be summarized using descriptive statistics by visit and by treatment group.

Vital signs collected after the first dose of treatment will be examined to determine the incidence of the following clinically relevant abnormalities.

Table 3: Vital Sign Criteria for Abnormality

Vital Sign Parameter	Criteria for Abnormalities
systolic blood pressure	>180 mmHg an increase from pre-dosing of more than 40 mmHg <90 mmHg a decrease from pre-dosing of more than 30 mmHg
diastolic blood pressure	>105 mmHg increase from pre-dosing of more than 30 mmHg <50 mmHg decrease from pre-dosing of more than 20 mmHg
pulse	>120 beats per minute an increase from pre-dosing of more than 30 beats per minute <50 beats per minute a decrease from pre-dosing of more than 20 beats per minute
temperature	>38.5°C and an increase from pre-dosing of at least 1°C
body weight	≥7% from Baseline value, or ≤7% from Baseline value

The number of subjects evaluated and the number and percentage of subjects with the defined abnormality at any time post-baseline will be presented by treatment group. The tabulation will use all the data up to the last visit of the Primary Assessment Phase including unscheduled visits and will also be repeated including the washout visits

Summary tables by treatment and timepoint will be provided for all vital signs parameters, with changes from baseline and percentage changes from baseline.

9.9.5. 12-lead Electrocardiogram Parameters

ECG measures as well as change from baseline will be summarized using descriptive statistics by visit and by treatment group. Boxplots for HR, QTcF, PR, QRS as well as changes from baseline will be produced for the trough values by treatment group. Similar boxplots will also be produced containing all timepoints on Week 8 by treatment group.

The analysis of the effect of dexpramipexole on ECG parameters (HR, QTcF, PR and QRS intervals) will be based on a mixed-effects repeated measures model with change-from-baseline (Δ) of the parameter (ΔHR, ΔQTcF, ΔPR and ΔQRS) as the dependent variable; time (i.e., post-baseline time point: categorical, using trough values only for Week 8); treatment (dexpramipexole and placebo); baseline and baseline by visit interaction and time by treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at post-baseline time points within subjects. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as

compound symmetry and autoregressive will be considered. From this analysis, the LS mean and 2 sided 90% CIs will be calculated for the contrast "dexpramipexole versus placebo" for each dose of dexpramipexole at each post-baseline time point.

The LS mean, standard error (SE), and 2-sided 90% CI from the statistical modeling for the change from baseline will be listed in the tables.

At the Week 8 visit, subjects will have 3 separate ECG assessments performed to evaluate potential cardiac drug interactions of albuterol and dexpramipexole. A separate summary will be presented for the Week 8 visit, containing the actual values, changes from baseline and also the changes from the Week 8 trough value.

ECG findings that are determined to be PCS will be summarized, examples of PCS ECG findings are given below:

The tabulation will use all the data up to the last visit of the Primary Assessment Phase including unscheduled visits.

Only potentially clinically significant ECG findings that were present on or after Day 1 and not present at baseline or screening will be tabulated.

List of Potentially Clinically Significant ECG Findings

Rate

Sinus bradycardia
Sinus tachycardia
Bradycardia
Tachycardia

Rhythm

Sinus arrhythmia
Premature atrial complexes
Ectopic atrial tachycardia
Paroxysmal supraventricular tachycardia
Premature ventricular complexes
Ventricular tachycardia
Bigeminy
Trigeminy
Wandering pacemaker
Multifocal atrial tachycardia
Sinus arrest
Premature junctional beat
Paroxysmal atrial tachycardia
Paroxysmal junctional tachycardia
Paroxysmal ventricular tachycardia
Torsade de Pointes
Ventricular flutter
Wolff-Parkinson-White Syndrome

Lown-Ganong-Levine Syndrome
Atrial fibrillation
Atrial flutter
Ventricular fibrillation

Conduction

First degree Atrioventricular (AV) block
Second degree AV block
Complete AV block
AV dissociation
Right bundle branch block
Left bundle branch block
Left anterior fascicular block
Left posterior fascicular block
Bifascicular block
Nonspecific intraventricular block
Wolf-Parkinson-White preexcitation
Sino atrial exit block
Wenckebach second degree AV block
Sick sinus syndrome
Mobitz second degree AV block

Wave

ST-T elevation
ST-T depression
T wave abnormality in inferior leads
T wave abnormality in anterior leads
RS transition zone displaced to right
Non-specific T wave abnormality
Non-specific ST-T elevation
Non-specific ST-T depression
QTc prolongation
Wide QRS
PR shortening
Poor R wave progression

Other Abnormality

Possible artifact
Possible myocardial Infarction (MI)
Old MI
Right atrial enlargement
Left atrial enlargement
Biatrial enlargement
Left ventricular hypertrophy
Right ventricular hypertrophy
Biventricular hypertrophy
Left axis deviation

Right axis deviation
Possible normal variant
Anteroseptal MI
Inferior MI
Pseudoinfarcts

The QT/QTc analysis approach will follow the ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.[5] The incidence of AEs potentially related to QTc increase will be presented for individual AEs and the incidence will be presented for the pool of any AEs potentially related to QTc increase. AEs potentially related to QTc increase will include: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, seizures, and others identified during a review of all AEs observed in the study.

For the evaluation of heart rate change, absolute heart rate, and changes from baseline by scheduled evaluation time will be tabulated by treatment group. The incidence of subjects with >120 beats per minute or an increase from pre-dosing of more than 30 beats per minute will be tabulated by treatment group. The incidence of AEs potentially related to heart rate increase will be presented for individual AEs and the incidence will be presented for the pool of any AEs potentially related to heart rate increase. A tabulation of AEs that could be linked to a heart rate effect of the drug will be presented with appropriate grouping of terms, e.g.:

a) Preferred terms: related to myocardial ischemia (angina, AMI, unstable angina, etc.)
b) Preferred terms related to congestive heart failure
c) Preferred terms related to tachycardia (atrial fibrillation, tachycardia, ventricular tachycardia, etc.)
d) Cardiac serious adverse events (SAEs) and relevant SAEs in the general System Organ Class (e.g., sudden death).

The maximum postdose QT and QTcF values in the Primary Assessment Phase will be summarized (number of subjects) by treatment according to the following categories:

Interval (ms)	Observed	> 450 ms
		> 480 ms
		> 500 ms
	Change from Baseline	> 30 ms
		> 60 ms

Summaries will also be produced for QT and QTcF fulfilling this criteria at each timepoint.

PR and QRS values will be summarized by treatment (number of subjects and number of time points) according to the following categories:

- ΔPR>25% AND a PR value >220 ms
- ΔQRS>25% AND a QRS value > 110 ms

Summaries will also be produced for PR and QRS fulfilling these criteria at each timepoint.

9.9.6. Protocol Deviations

Potential protocol deviations (PDs) are identified programmatically (using EDC data) and manually (by the clinical and medical team members) utilizing the criteria specified in the *AS201 Study Specific Protocol Deviation List*. Potential PD are tracked as a [redacted] in [redacted] which automatically assigns each a unique ID. Each [redacted] is reviewed [redacted] to confirm if the potential PD may be valid. A [redacted] determined not to be valid is so designated and archived in the [redacted] system.

After review, a valid PD is assigned [redacted] status = closed, then assigned to one of the following PD categories/sub-categories.

Table 4: Protocol Deviations

Category	Subcategory	Important	Not Important
Inclusion / Exclusion Criteria	1. Eligibility criteria not met	x	
Informed Consent	2. Administrative/operational informed consent error		x
Informed Consent	3. Failure to consent using updated informed consent form		x
Informed Consent	4. Informed consent not obtained	x	
Investigational Product	5. Dispensing error		x
Investigational Product	6. Dosing adherence <80%	x	
Investigational Product	7. Missed observing study drug administration in clinic		x
Investigational Product	8. [redacted] bottle assignment incorrect		x
Investigational Product	9. Study drug not dispensed to subject	x	
Investigational Product	10. Subject received the incorrect treatment	x	
Investigational Product	11. Administrative/operational drug accountability error		x
Study Conduct / Procedures	12. Non-compliance with documenting of AE/SAE/Pregnancy	x	
Study Conduct / Procedures	13. AEC not collected	Baseline, Week 8, and Week 12	other visits
Study Conduct / Procedures	14. AEC not collected within window	Baseline, Week 8, and Week 12	other visits
Study Conduct / Procedures	15. FEV1 not collected	Baseline, Week 8, and Week 12	other visits
Study Conduct / Procedures	16. FEV1 procedure performed incorrectly	Baseline, Week 8, and Week 12	other visits
Study Conduct / Procedures	17. FEV1 procedure performed out of window		x
Study Conduct / Procedures	18. Other procedure not performed		x
Study Conduct / Procedures	19. Other procedure performed incorrectly		x

Category	Subcategory	Important	Not Important
Study Conduct / Procedures	20. Other procedure performed out of window		x
Study Restrictions	21. Non-compliance with Concomitant Therapy Restrictions / Requirements		x
Withdrawal Criteria	22. Subject met discontinuation criteria but was not discontinued	x	

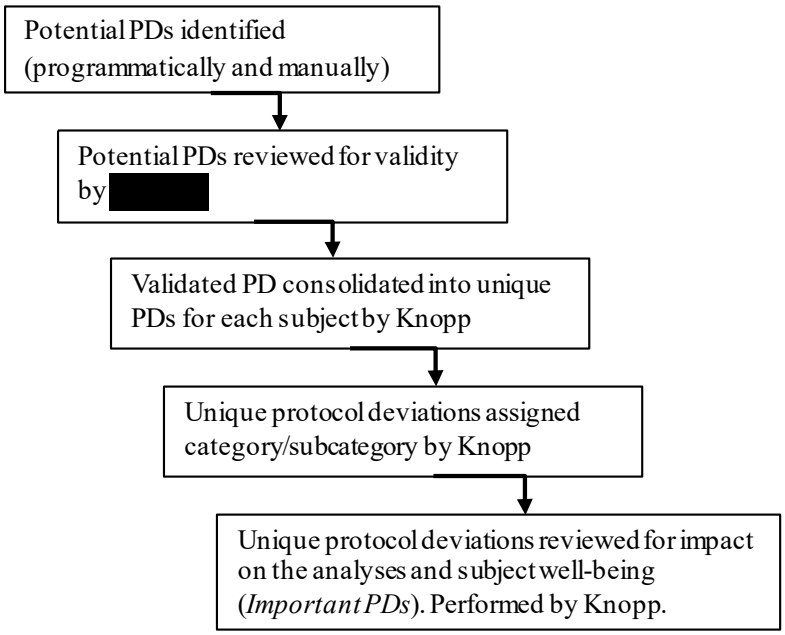
Following the assignment of category and subcategory, each PD is assessed to assure the designation as Important or Not Important is valid. Important designation depends on the event having impinged on subject safety, subject well-being, or trial data.

During execution of this clinical trial, procedural restrictions due the COVID-19 global pandemic were implemented for subject and site personnel protection. Spirometry, FeNO, and nasal/pharyngeal swab collection were temporarily discontinued from March 2020 to May 2020. PD resulting from these exigencies are additionally identified

All PD will be listed in the CSR by subject and timepoint of occurrence and will specify if related to COVID-19 study restrictions. Important PD will be summarized by deviation type and by treatment assignment and will specify if related to COVID-19 study restrictions.

Prior to the interim analysis, an attempt will be made to identify and characterize PD for the 'all subjects' population (e.g., all subjects who signed the ICF and had any study assessment recorded in the database).

Figure 3: Protocol Deviation Processing



9.9.7. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The definition of hematologic responder was modified from the original protocol definition of "≥90% reduction of blood eosinophil count, from Baseline to Week 12" to "Week 12 blood eosinophil count of $\leq 0.05 \times 10^9$/L". The change was made to define the responder group more closely with the known pharmacodynamics of the drug.

Several subjects missed Pulmonary Function Tests due to COVID-19. For the analysis of pulmonary function tests the MMRM analysis will exclude subjects if they were missing both Week 8 and week 12 FEV1 due to COVID-19. Dexpramipexole is unlikely to show an effect on FEV1 at the week 4 visit and including only week 4 data may bias results against dexpramipexole. Normally it is inappropriate to exclude subjects with missing data from the analysis but when the exclusion is because they missed the evaluation because of COVID-19 that should not introduce bias. Subjects who are missing FEV1 due to other reasons will be included in the analysis

For the analysis of ACQ-7 (which includes an FEV1 item) the MMRM analysis will exclude subjects if they were missing both Week 8 and week 12 FEV1 due to COVID-19.

To control the alpha level for testing 3 dose groups versus placebo for the primary endpoint and for testing FEV1, a closed hierarchical testing procedure was originally planned to be in the following order:

1. First, the 300mg/day dose group will be tested versus placebo for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
2. the 150 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
3. the 75 mg/day dose group will be tested versus placebo at the 0.05 level for change in blood absolute eosinophil count at Week 12, and if this reaches the <0.05 level then,
4. the pooled 150 and 300 mg/day dose groups will be tested versus placebo at the 0.05 level for change in FEV1 at Week 12.

the pooled 150 and 300 mg/day dose groups analysis of change in FEV1 at Week 12 was moved up to the 3rd test and the 75 mg/day dose group tested versus placebo was moved down to the 4th test.

For all the covariate adjustment analyses, GINA treatment steps 3-5 will be used as a categorical variable with 3 levels (3,4,5) instead of two levels 3 vs. 4/5 because each of the 3 levels may have a different prognostic level for the outcome measures.

An analysis of the proportion of subjects with an AEC of $\leq 0.05 \times 10^9$/L and for proportion of subjects with a ≥ 90% reduction of AEC will be performed using GEE to obtain the estimated treatment effect at Week 12. Similar analyses will also be performed for the proportion of subjects with a ≥12% increase in FEV1 and the proportion of subjects with a change from baseline in ACQ-6 score ≤-0.5.

Specific criteria defining the per-protocol population were included in section 7.5 of the current SAP.

During the course of the trial consensus guidelines for the standardization of spirometry were updated. The updated guidelines were used to grade FEV1 results. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST

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12. APPENDICES

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