Statistical Analysis Plan

Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron Emission Tomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma

Study Number C38072-AS-40105 (or CEP38072-AS-40105)

NCT02937168

Statistical Analysis Plan Approval Date: 30 May 2017

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Phase 4

BLA number: 761033

Approval Date: 30 May 2017

Sponsor

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
United States

Prepared by: [redacted]
KEYRUS Biopharma

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **CEP38072-AS-40105**

Study Title: **Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron EmissionTomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma**

Statistical Analysis Plan for:

☐ **Interim Analysis** ☐ **Integrated Summary of Efficacy**

☒ **Final Analysis** ☐ **Integrated Summary of Safety**

Amendment: **<x.x >**

Author: [redacted] **Date** 26 May 2017

Approver: [redacted] **Date**

[redacted]

Approver: [redacted] 30 MAY 2017

Approver: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AQLQ	Asthma Quality of Life Questionnaire
BMI	Body mass index
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DPP4	Dipeptidyl peptidase 4
ECG	Electrocardiogram/Electrocardiography
FEF	Forced Expiratory Flow
FeNO	Fractional exhaled Nitric Oxide
FEV	Forced Expiratory Volume
FDG	Fludeoxyglucose F 18
FVC	Forced Vital Capacity
GLG	Global Lung Glycolysis
HC	Healthy control
IgE	Immunoglobulin E
ITT	Intent-to-Treat
LP	Lung Parenchyma
MedDRA	Medical Dictionary for Regulatory Activities
PCSA	Potentially clinically significant abnormal
PEFR	Peak Expiratory Flow Rate
PET/CT	Positron Emission Tomography/Computed Tomography
PP	Per-Protocol
R&D	Research and Development
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TARC	Thymus and Activation Regulated Chemokine

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc study CEP38072-AS-40105, (Distribution of Eosinophils in Asthma after Reslizumab (DEAR). A 7-week, Placebo-Controlled, Double-Blinded, Parallel-Group, Imaging Study Using Positron Emission Tomography/Computed Tomography (PET/CT) to Characterize the Effect of Intravenous Reslizumab on Airway Inflammation in Patients with Eosinophilic Asthma), and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

The reader of this Statistical Analysis Plan is encouraged to read the study protocol for details on the conduct of this study, the operational aspects and times of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints).When differences exist in descriptions or explanations provided in the study protocol and this Statistical Analysis Plan, the Statistical Analysis Plan prevails; the differences will be explained in the Clinical Study Report.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

1.1.1 Primary Objectives and endpoints

This study is designed in two parts: Part 1 is validation of PET/CT scan and Part 2 is evaluation of the effect of reslizumab on inflammation in the lungs. There are 2 related primary objectives of this study:

- To establish that positron emission tomography (PET)/computerized tomography (CT) imaging of the lung can reliably distinguish healthy control (HC), non-asthmatic subjects and patients with severe asthma with an eosinophilic phenotype (Part 1: initial validation of PET/CT scan).
- If the utility of PET/CT scanning is established as per objective 1 (Part 1): Part 2 objective is to show that reslizumab produces a reduction in signal intensity (reduction in lung inflammation) in patients with severe asthma with an eosinophilic phenotype (Part 2: evaluation of the effect of reslizumab vs placebo in reducing inflammation).

For primary objective 1 (Part 1), a ≤10% variability between the first and second measurements of PET/CT scans as measured by global lung glycolysis (GLG) within each group [HCs (n=5) and patients with asthma (n=10)] will be considered as the maximum allowed variability. This criterion is a measure of intra-group reproducibility. At this point (i.e. establishing intra-group reproducibility), healthy subjects are considered completed.

A ≥5% difference in GLG between HC subjects and patients with eosinophilic asthma, based on the average of the 2 measurements of PET/CT, will be selected as minimal difference that validates the ability PET/CT to differentiate these 2 populations of study participants. This criterion is a measure of inter-group reproducibility.

Only after these intra- and inter-group variability criteria of Part 1 are met, the patients with asthma will be considered eligible to enter Part 2 of the study and randomly assigned in double-blind fashion to receive either placebo (n=5) or reslizumab (n=5). If these exploratory criteria (Part 1) are not met (8 or more asthma patients do not meet the criteria to enter Part 2 of the protocol), the study will be reevaluated.

For primary objective 2 (Part 2), the primary efficacy endpoint is the change from baseline to week 4 in global lung glycolysis (GLG) (i.e., ΔGLG).

The supportive primary efficacy endpoint is the change from baseline to week 4 in lung parenchyma (LP) standardized uptake value (SUV) mean.

1.1.2 Secondary Objectives and endpoints

The secondary objectives of the study are to demonstrate a correlation between the benefit observed on imaging (PET/CT) with:

- reductions in blood eosinophil counts
- improvement in clinic visit lung function
- reductions in fractional exhaled nitric oxide (FeNO)
- improvements in Asthma Quality of Life questionnaire (AQLQ) scores.

The secondary efficacy endpoints are:

- the change from baseline to week 4 in blood eosinophil counts
- the change from baseline to week 4 in FEV1
- the change from baseline to week 4 in FeNO
- the change from baseline to week 4 in AQLQ.

1.2. Exploratory/ Safety Objectives and Endpoints

1.2.1. Exploratory Objectives and endpoints

Exploratory objectives are:

- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and serum biological markers of asthmatic inflammation
- to demonstrate a correlation between changes in the lung PET/CT signal produced by reslizumab and other lung function variables including forced vital capacity (FVC), peak expiratory flow rate (PEFR) and forced expiratory flow at the 25% point to the 75% point of forced vital capacity (FEF25%-75%)
- to demonstrate that reslizumab produces greater reductions in inflammation of upper-body lymph nodes and bone marrow than placebo as seen on PET/CT
- for those patients that can produce sputum, to demonstrate an association between changes in sputum eosinophil numbers produced by reslizumab and the lung PET/CT signal produced by reslizumab.

In this study, we wish to determine whether any changes in the levels/quantity of the following biomarkers occur following the administration of reslizumab:

- biological markers of inflammation and asthma (blood):
  - IgE in peripheral blood

  - DPP4 in peripheral blood
  - 25-hydroxy vitamin D in peripheral blood
  - eotaxin-1, -2, and -3 in peripheral blood
  - TARC in peripheral blood
  - MCP-1 and MCP-4 in peripheral blood
  - ILC2 in peripheral blood
- lung function variables:
  - FVC
  - PEFR
  - FEF25%-75%
- the uptake of FDG in the lymph nodes and bone marrow as measured by the PET-CT imaging parameters indicated for the primary efficacy variable.
- sputum eosinophils for those patients that can produce sputum.

Blood samples for assessment of these exploratory biomarkers will be collected and processed using the procedures in place at the investigational center [redacted]. For more detailed descriptions, see section 8.1 of the protocol.

1.2.2. Safety endpoints

The safety endpoints are:

- occurrence of adverse events throughout the study
- vital signs (blood pressure, pulse, respiratory rate, body temperature, and blood oxygen saturation (SpO2)) throughout the study
- clinical laboratory evaluations throughout the study
- physical examination findings throughout the study
- use of concomitant medication throughout the study.

1.3 Immunogenicity Objectives and Endpoints

Blood samples for assessment of anti-drug antibodies (ADA) response in Part 2 will be collected from reslizumab-treated patients at scheduled visits at baseline (before dosing, V4) and after dosing at weeks 2 and 6 (visits 5 and 7) only. Unscheduled blood samples for anti-reslizumab antibody assessments will also be collected from reslizumab-treated patients with asthma upon experiencing a severe hypersensitivity reaction (e.g. anaphylaxis).

2. STUDY DESIGN

2.1. General Design

This is a 7-week, single-center, randomized, double-blind, placebo-controlled, parallel-group study using PET/CT to evaluate the effect of reslizumab administered at 3.0 mg/kg in adult patients with eosinophilic asthma. The study will consist of a screening period (up to 21 days), a 6-week, double-blind treatment/assessment period, and a follow-up telephone contact (7±3 days after last visit).

All subjects who participate in this study will consent at the investigational center [redacted] prior to undergoing any study procedures. After consent is obtained, all participants will undergo all tests and procedures required for eligibility, including sputum and blood eosinophil level assessments. Patients with asthma (does not apply to HC subjects) must have a screening blood eosinophil count of ≥400 cells/μL to be included. A maximum of 3 screening blood eosinophil assessments will be conducted. If the first assessment yields a blood eosinophil level below 400 cells/μL patients with asthma may return for a second assessment of blood eosinophil level after 7 days. A third and final assessment will be performed 7 days after the second assessment, if necessary (e.g., if the blood eosinophil level remains <400 cells/μL at the second assessment).

The patients must maintain their usual asthma controller regimen without change throughout the screening and study periods. A patient who experiences an asthma exacerbation during this time that requires additional medication, beyond increased SABA use, will be considered to have failed screening and cannot undergo randomization. A patient may be rescreened for this reason 1 time only. If a patient experiences an asthma exacerbation requiring treatment with systemic steroids, they will only be allowed to be rescreened 6 weeks after completion of treatment. All patients that have to be rescreened must be stable on other asthma medications for 30 days prior to rescreening.

This study is designed in 2 parts. Part 1 is a validation step whereby the sponsor wishes to determine (1) the intra-patient reproducibility in the GLG measure, and (2) the difference in the GLG measure between individual patients with severe asthma with an eosinophilic phenotype (1-by-1) and the entire HC group. Limits for both the reproducibility within patients and difference between the 2 groups have been provided by subject matter experts. Part 2 will be a 7-week double-blind evaluation of patients with severe asthma with an eosinophilic phenotype that have been randomized to receive a single dose of either placebo or reslizumab at 3 mg/kg.

Part 1

Within 7 days (±3 days) of eligibility being confirmed, participants will have a PET/CT scan as per the PET/CT scan protocol described in Part 2 below. Participants will return to the [redacted] 7 days (±3) after the first PET/CT scan (taken during visit 2) for a second PET/CT scan following the same procedures described above. HC subjects (n=5) may also have a second sputum induction and blood sample collection at [redacted] within 1 day of the second PET/CT scan, if feasible (preferred but not required). Healthy subjects will be considered complete at this time. Only after all 5 HCs have completed the study will patients with asthma be screened.

If the relative difference in GLG (based on the average of the 2 measurements) between healthy subjects and asthma patients will be ≥5%, then the asthma patients will be randomized. A 10%

variability (measured as relative difference between first measurement and second measurement) between PET/CT scans as measured by GLG within each group will be considered as the maximum allowed variability. The Part 1 criteria have been set at these levels to observe a difference between the healthy subjects and patients with asthma and to ensure intra-group reproducibility. The criteria are based on the investigators' prior experience. If these exploratory criteria are not met (i.e., 8 or more asthma patients do not meet the criteria to enter Part 2 [inclusion criteria k and l]), then the study will be reevaluated.

Detailed by-visit information for Part 1 are provided in sections 3.14.1 and 3.14.2 of the protocol.

Part 2

If eligible (i.e., if inter- and intra-group GLG variability criteria are met), patients will be randomized. This may occur at any time after confirmation of eligibility and up to the time of dosing. Patients will return to [redacted] for baseline clinical, serological, and biochemical measures at the Clinical Research Center (CRC) according to standard procedures. Once these are completed, patients will randomly receive either placebo or reslizumab and will receive the infusion at [redacted]. Any new serious adverse events, reslizumab-related adverse events, and new concomitant medications will be reported.

All planned PET/CT scans (weeks 2, 4, and 6) should be scheduled at the time of randomization. Within 2 weeks (±3 days) of the infusion, patients will return to [redacted] for clinical tests and procedures. Within 3 days of this visit, patients will undergo a PET/CT scan at the [redacted]. Patients repeat the clinical tests and procedures at weeks 4 and 6 post-infusion. Each visit at [redacted] will be followed by a PET/CT scan at the [redacted] as described above.

Schematic presentation of the study design for Part 1 and Part 2 is given in Figures 1, 2, and 3, section 3.1 of the protocol.

The assessments and procedures performed during each study visit are detailed in Table 1 below and in Section 3.14 of the protocol. Detailed by-visit informations for Part 2 are provided in section 3.14.3 of the protocol. Detailed description of each assessment is provided in section 6 (for efficacy), section 7 (for safety), and section 8 (other assessments) of the protocol.

If a patient elects to withdraw (or is discontinued from treatment by the investigator), every attempt will be made to continue the assessments subsequent to his/her withdrawal from the study (see Table 1 above and section 3.14 of the protocol).

Table 1. Study Procedures and Assessments

Study period	**Pretreatment**	**Phase 1**		**Phase 2**				**Follow-up**
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Allowed time windows	**Up to -21 days**	**0 days**	**±3 day(s)**	**Within 3 days of V3**	**±3 day(s)**	**±3 day(s)**	**±3 day(s)**	**Up to +7 day(s)**
Procedures and assessments	**Screening** [redacted]	**Baseline (day 1)** [redacted]	**W1 (day 7)** [redacted]	**Baseline (day 1)** [redacted]	**W2 (day 14 from V4)**	**W4 (day 28 from V4)**	**W6 (day 42 from V4)/early termination**	**W7**
Informed consent	X	X						
Medical history	X							
Smoking history	X							
Prior medication and treatment history	X							
Complete physical examination[b]	X						A	
Brief physical examination[b]				A	A	A		
Vital signs measurement[bc]	X			A	A	A	A	
Inclusion and exclusion criteria	X	X						
Clinical chemistry[bd]	X	X	X	A	A	A	A	
Urine/serum β-HCG test for women of child bearing potential[be]	X							
Hematology (eosinophils)[f]	X			A	A	A	A	
Sputum sampling for eosinophils[g]	X			A	A	A	A	
Urinalysis[h]	X						A	
PET/CT scan [redacted] [i]		X	X		A	A	A	
ACQ-6 for entry criterion	A							
Electrocardiography[b]	X							

Study period	**Pretreatment**	**Phase 1**		**Phase 2**				**Follow-up**
Visit number	**V1**[a]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Allowed time windows	**Up to -21 days**	**0 days**	**±3 day(s)**	**Within 3 days of V3**	**±3 day(s)**	**±3 day(s)**	**±3 day(s)**	**Up to +7 day(s)**
Procedures and assessments	**Screening** [redacted]	**Baseline (day 1)** [redacted]	**W1 (day 7)** [redacted]	**Baseline (day 1)** [redacted]	**W2 (day 14 from V4)**	**W4 (day 28 from V4)**	**W6 (day 42 from V4)/early termination**	**W7**
Spirometry	X			A	A	A	A	
ADA[bj]				A	A		A	
Blood collection for biomarker analysis				A	A	A	A	
AQLQ				A	A	A	A	
Randomization				A				
Study drug infusion				A				
Adverse event inquiry	X	X	X	A	A	A	A	A
Concomitant medication inquiry	X	X	X	A	A	A	A	A

[a] Screening visit (visit 1) will take place up to 21 days before the V2 visit. It is understood that not all procedures can be completed on the same day. In particular, the patient may need to return to satisfy the medication hold for screening pre-bronchodilator FEV_1.

[b] Physical examination, vital signs, blood samples, and ECG should be obtained before spirometry procedures and IP administration.

[c] Vital signs measurements will include blood pressure, pulse, respiratory rate, body temperature, and blood oxygen saturation (SpO_2). Height and weight measurements are required only at screening visit.

[d] The clinical chemistry will include a complete metabolic panel.

[e] A serum β-HCG pregnancy test will be administered at V1 only, for all participating women of childbearing potential. Urine β-HCG tests will be performed for all participating women of childbearing potential, at V2, V3, V5, V6, and V7, prior to performance of PET/CT scan.

[f] Hematology will include a complete blood count with differential. The results of the differential blood tests performed after drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.

[g] The results of the sputum eosinophil assessments performed after study drug administration will be blinded. If there is a medical need to review these results, the investigator will contact the medical monitor.

[h] A complete urinalysis will be performed at the screening visit, visit 4, and visit 7; a urine dipstick test for glucose will be performed prior to each PET/CT scan.

[i] Patients should be observed for 1 hour following completion of PET/CT scan.

[j] Blood samples for ADA assessment will be collected at baseline (before study drug administration) and other scheduled time points, and upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).

[k] Randomization can occur any time from determining that the patient qualifies for Part 2 up to study drug infusion. Patient qualification is based on meeting both of the following 2 steps: 1) ΔGLPG ≤10% versus V2 [for reproducibility] and 2) ΔGLPG≥5% versus HC [for signal] to study drug infusion.

A=patients with asthma only; ACQ-6=6-item Asthma Control Questionnaire; ADA=anti-drug antibodies; AQLQ=Asthma Quality of Life Questionnaire; β-HCG= beta human chorionic gonadotropin; CBC=complete blood count; CT=computerized tomography; HC=healthy control subjects only; PET=positron emission tomography; V=visit; W=week; X=patients with asthma and healthy control subjects

2.2. Randomization and Blinding

This is a randomized, double-blinded, placebo-controlled, parallel-group study. After the 2 baseline PET/CT scans and successful completion of all requirements (Part 1), patients will be randomly assigned 1:1 in a double-blind fashion to receive either placebo or iv 3.0 mg/kg reslizumab. In order to maintain the blind, each patient will be assigned a unique identifier number and all reference to the patient will be by using this identifier.

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. The output of the randomization process will be a patient randomization list.

The sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis and the treatment assignment is revealed, with the exception of the bioanalytical group who will not be blinded to facilitate ADA sample analysis and an un-blinded person who will be responsible for randomization assignment. Additionally, in order to maintain the study blind, blood and sputum eosinophil levels assessed after study drug administration will not be available to investigators, their blinded staff, the sponsor, and blinded members of the clinical research organization. There will be un-blinded data management, un-blinded site staff, and an un-blinded CRA who will not sit on the study team and be responsible for un-blinded eosinophil data.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on the case report form (CRF). The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Treatment assignment should not be recorded in any study documents or source document.

At the time of analysis (after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded treatment assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

2.3. Data Monitoring Committee

Data Monitoring Committee will not be used during this study

2.4. Sample Size and Power Considerations

This study is exploratory in nature; therefore, no formal hypothesis testing is planned. Based on clinical and practical considerations, 5 healthy subjects and 10 eosinophilic asthma patients (5 patients treated with reslizumab, and 5 patients treated with placebo) is considered adequate for:

1. a validation of the ability of PET/CT to differentiate patients with eosinophilic asthma from HC subjects,
2. an evaluation of the effect of reslizumab versus placebo on inflammation of the lungs.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.5.2. Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of study as defined in the study protocol. This Statistical Analysis Plan and any corresponding amendments will be approved before database lock, in accordance to SOP GBP_RD_702 (Statistical Analysis Plan).

The randomization codes will not be unblinded until this Statistical Analysis Plan has been approved and issued.

3. ANALYSIS SETS

3.1.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients (Part 2). In this analysis set, treatment will be assigned according to the treatment to which patients were randomized, regardless of which treatment they actually received. This analysis set will be used for the analysis and summarization of primary efficacy and supportive primary efficacy and secondary efficacy endpoints, for summarization of patients demographics (Summary 15.1.2.2) and patients baseline characteristics (15.1.2.4) for Part 2 and also, for summarization and listing of protocol violations for Part 2 (Summary 15.1.7.2).

3.1.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug/placebo. In this analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized.

The safety analysis set will be used for safety analyses of Part 2 of the study. In addition, safety analyses may present safety data from both Part 1 based on all enrolled analysis set (section 3.1.4) and Part 2 of the study based on the safety analysis set, as deemed necessary.

3.1.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the ITT analysis set who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. This analysis set will be used for summarization and reporting of all efficacy endpoints and also for exploratory endpoints (Part 2).

3.1.4. Enrolled Analysis Set

The enrolled analysis set will include all participants enrolled to Part 1 of the study, including healthy subjects and patients with eosinophilic asthma. This analysis set will be used for establishing initial validation of PET/CT scan (Part 1), summarization and reporting of study participants (HCs and patients) disposition (Summary 15.1.1.1), study participants demographics (Summary 15.1.2.1) and baseline characteristics data (Summary 15.1.2.3) of Part 1 and also, for summary and listing of protocol violations for all study participants (Part 1) (Summary 15.1.7.1).

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), median, minimum, and maximum.

Descriptive statistics for categorical variables include patient counts and percentages (n, %). Categories for missing data will be presented if necessary.

Correlation will be calculated using Spearman's Rho correlation.

4.2. Specification of Baseline Values

For Part 2, baseline is the last observed data before the first dose of study drug (i.e, Visit 4, Day 1), unless otherwise noted. For assessing changes from baseline in PET/CT signal as surrogate of lung inflammation in patients with asthma at each post-randomization visit, the baseline is the average of two measurements at visits 2 and 3 of Part 1. See Table 1 (section 2.1).

4.3. Handling Withdrawals and Missing Data

Overall mean scores for AQLQ (Asthma Quality of Life Questionnaire at each visit of Part 2) and ACQ-6 (6-item Asthma Control Questionnaire for entry criterion at Screening for patients with asthma only) will be calculated for patients who answer all the questions. For the item analysis, the mean of the score by domain will be computed if all questions of the domain are answered.

For the AQLQ questionnaire, if a lot of missing data are observed, it will be dealt with by imputing mean values where more than half of the responses to a subscale will be present, as sensitive analysis (Apfelbacher et al. 2012).

For all other variables, only the observed data from the evaluable patients/subjects up to study completion or study withdrawal will be used in the statistical analyses, i.e., there is no plan to impute missing data for other variables.

4.4. Study Days and Visits

For by-visit summaries, if there are multiple assessments at a post baseline visit then the last non-missing assessment at that visit will be used for the summary (this includes scheduled and unscheduled assessments).

Study days are numbered relative to the first day of study drug administration. The start of treatment (Day 1, Visit 4) is defined as the date on which a patient takes the first dose of study drug, as recorded on the study drug diary. Days will be numbered relative to treatment start (i.e., ..., –2, –1, 1, 2, ...; with day 1 being the first day of study drug administration and day –1 being the day before the first day of study drug administration). For details of study days and visits, see Table 1.

5. STUDY POPULATION

5.1. General

With the exception of brief physical examination reported in Part 2 only (see Table 1), where only ITT analysis set will be used and ACQ-6 questionnaire used for entry criteria at Screening for patients with asthma only, all analyses detailed in section 5 will be based on the enrolled analysis set (Part 1) and on the ITT analysis set (Part 2) as well, unless otherwise specified.

For analysis performed on the enrolled analysis set, summaries will be presented by study participants status (Healthy Control Subjects (HCs), n=5)) vs. patients with asthma, n=10) and overall (n=15).

For analysis performed on the ITT analysis set, FAS or safety set summaries will be presented by treatment group (reslizumab (n=5) vs. placebo, n=5)) and overall (n=10).

5.2. Patient Disposition

For Part 1, data from patients screened, subjects/patients enrolled, not enrolled (i.e., screen failure and reason for failure), subjects/patients completed Part 1, subjects/patients who withdraw from Part 1 with reason for withdrawal. For Part 2, patients enrolled but not randomized (and reason for not randomized), patients who are randomized (ITT analysis set), patients randomized but not treated, safety, and full analysis sets, patients who complete the study and patients who withdraw from the study with reason for withdrawal, will be summarized using descriptive statistics (Summary 15.1.1.1).

5.3. Demographics and Baseline Characteristics

Patients and HC subjects demographics: age (years), sex (male , female), height (cm), weight (kg), body mass index (BMI, kg/m^2), ethnicity (Not Hispanic or Latino, Hispanic or Latino, unknown) , race (white, black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, other), and baseline characteristics including tobacco usage: smoker or not, current or former user (never used, formerly used, currently uses), number of non-smoking years, number of smoking years, number of packs per days, will be summarized for Part 1 based on the enrolled analysis set (Summaries 15.1.2.1 and 15.1.2.3) and for Part 2 based on the ITT analysis set (Summaries 15.1.2.2 and 15.1.2.4), using descriptive summary statistics.

Airway reversibility testing using spirometry will be summarized for Part 1 using the enrolled analysis set and for Part 2 using the ITT analysis set (Summaries 15.1.3.1 and 15.1.3.2, respectively).

Similarly, clinical laboratory tests (see Table 4 of the protocol) performed at screening visit will be summarized for serum laboratory chemistry tests, serum laboratory hematology tests, and urinalysis laboratorty tests based on the enrolled analysis set (Summaries 15.1.4.1, 15.1.4.2, and 15.1.4.3, respectively).

Serum β-HCG test performed at screening will be summarized (n, %) by beta-HCG category (negative, borderline, and positive) and participants group (HCs, asthma patients) based on enrolled analysis (Summary 15.1.4.4). Positive/borderline values will be listed by individual participants for the enrolled analysis set.

Vital signs at screening visit, including pulse rate, systolic/diastolic blood pressure, respiratory rate, temperature and oxygen saturation, will be summarized, by participants group (HCs, asthma patients), for enrolled analysis set (Summary 15.1.5.1).

Moreover, number and percentages of patients/subjects (Part 1) with at least one abnormal physical examination finding at screening visit will be summarized, by participants group and overall, based on the enrolled analysis set (Summary 15.1.6.1). Similarly, for Part 2, number and percentages of patients with at least one abnormal physical examination finding at each visit will be summarized by visit (4, 5, 6, and 7) and treatment group (reslizumab, placebo and overall) based on the safety analysis set (Summary 15.3.4.1).

Any physical examination finding that is judged by the investigator as clinically significant will be considered as an adverse event and listed as such.

5.4. Medical History

All medical history will be coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of general medical history abnormalities will be summarized using descriptive statistics (n, %) by system organ class (SOC) and preferred term. Patients/subjects are counted only once in each preferred term and SOC category. Summaries will be presented by study participants group (Asthma patients versus HC subjects) and overall (Summary 15.1.7.1) based on the enrolled analysis set, and by treatment group (Reslizumab versus Placebo) and overall (Summary 15.1.7.2) based on safety analysis set.

Asthma/allergic history are recorded on the CRF. The incidence of following asthma/allergic histories (asthma, chronic sinusitis, atopic dermatitis, aspirin rhinitis, ever received allergy shots, presence of pets at home, food allergy, eosinophilic esophagitis, asthma exacerbations requiring systemic corticosteroids within the last 12 months, patient was hospitalized or visited the emergency department for asthma within the last 12 month, history of intubation for asthma exacerbation, history of ICU admission for asthma exacerbation, days missed from school/work due to asthma in the last 12 months) will be summarized, by study participants group, based on the enrolled analysis set (Summary 15.1.7.3) and by treatment group, based on the safety analysis set (Summary 15.1.7.4), using descriptive statistics. Patients are counted only once in asthma/allergic histories.

The anteriority of the first diagnosis and of the most recent event and the number of events will be summarized by asthma/ allergies history abnormalities.

The ACQ-6 is a validated asthma assessment tool performed at Screening (Visit 1) as entry criterion six questions self-assessments questionnaire completed by the patients only. The Healthy subjects do not use this tool. Each question on the ACQ-6 is scored on 7-point scale ranging from 0 to 6, and the total score is the mean of all responses (see Appendix A of the protocol and Juniper et al (1999)). The total score will be summarized, by treatment group, based on the ITT analysis set using descriptive statistics (Summary 15.1.7.5).

Nasal polyps history are recorded on the CRF. The incidence of nasal polyps history abnormalities will be summarized using descriptive statistics (n, %). Patients/subjects are counted only once. Sinus surgery performed (Y/N), anteriority of the surgery (years), diagnosed by CT scan (Y/N), anteriority of the CT scan (years) and anosmia will be summarized, by study participants group based on the enrolled analysis set for Part I (Summary 15.1.7.6), and by treatment group based on the safety analysis set for Part II (Summary 15.1.7.7), using descriptive statistics.

5.5. Prior therapy and Medication

Any prior medication, treatment, or procedure a patient/subject has had within 4 weeks before screening and stopped before the first study visit (screening) will be recorded on the CRF.

Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the latest version of the World Health Organization drug dictionary (WHO Drug)

The incidence of prior therapies and medications will be summarized using descriptive statistics (n, %) by therapeutic class and preferred term and study participants, based on the enrolled analysis set for Part I (Summary 15.1.8.1), and by therapeutic class/preferred term and treatment group based on the safety analysis set for Part II (Summary 15.1.8.2). Patients/subjects are counted only once in each therapeutic class category, and only once in each preferred term category. Prior therapies and medications will include all medications taken and therapies administered before the first day of study drug administration.

For details of allowed prior medications (with restrictions) and not allowed medications during the study, see section 5.3 of the protocol.

5.6. Electrocardiography

A 12-lead ECG values collected at Screening (ECG mean hear rate, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, and RR interval) and the proportion of normal ECG, non-clinically significant abnormality and clinically significant abnormality at screening will be summarized, by study participants group and overall based on the enrolled analysis set (Summary 15.1.9.1) and safety analysis set (Summary 15.1.9.2), using descriptive statistics (n, %).

5.7. Childbearing Potential and Methods of Contraception

For female patients, information related to childbearing potential, and menopause will be collected. Childbearing potential (Y/N), birth control method [combined (estrogen and gestagen) oral contraceptives, hormone implants, hormone rings, contraceptive patch, hormones injectables, progesterone only hormonal contraception, other] , barrier methods of contraception (diaphragm with spermicide, portio cap with spermicide, condoms with spermicide, other), intrauterine device (copper, hormonal, none), abstinence (Y/N), surgically sterilized (Y/N), menopause age, documented hysterectomy (Y/N), bilateral oophorectomy or salpingectomy (Y/N) will be summarized, using descriptive summary statistics, by study participants group and overall based

on the enrolled analysis set (Summary 15.1.10.1), and by treatment group and overall based on the safety analysis set (Summary 15.1.10.2).

A serum β-HCG pregnancy test will be performed at V1 (Screening) only, for all participating women of childbearing potential. Data will be summarized (n, %) by beta-HCG category (negative, borderline, and positive) and participants group (HCs, asthma patients) based on enrolled analysis (Summary 15.1.4.4), and will be listed.

Urine β-HCG tests will be performed, for all participating women of childbearing potential, at V2, V3, V5, V6, and V7, prior to performance of PET/CT scan and will be listed.

5.8. Study Protocol Violations

Subjects/patients with any protocol violations (as recorded in protocol violation CRF) during the study will be summarized by violation classification category and overall using descriptive statistics (n, %) for the enrolled analysis set (Part 1: Summary 15.1.11.1) and for the ITT analysis set (Part 2: Summary 15.1.11.2). Subjects/patients will be counted only once in each violation category for the summary purpose. Data will be listed.

All instances of medication errors, overdose, misuse, abuse, off-label use, and occupational exposure will be summarized in category “Non-Compliance to study investigational medical product (IMP).”

For definition of protocol violations, see sections 11.1.2 and 7.3 of the protocol.

6. EFFICACY ANALYSIS

6.1. General

The study is composed of two parts with two primary objectives.

The enrolled analysis set will be used for the part 1 analysis (summaries and listings). Summaries will be presented by participants status [HC subjects (n=5) vs. patients with asthma (n=10)] and overall.

The ITT analysis set will be used for the summaries and presentations of the primary and secondary efficacy endpoints and the FAS analysis set will be used for all efficacy and exploratory analyses for the Part 2 data. Summaries will be presented by treatment group (reslizumab vs. placebo) and overall.

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

The primary efficacy measure for this study is the change in GLG as assessed by PET/CT.

Part 1 of the study will validate this measure by comparing this assessment between HC subjects and patients with eosinophilia asthma.

In Part 1, the primary efficacy endpoint is the intra-patient variability (reproducibility measurement) in each group and inter-group variability between HC group and individual patients with eosinophilic asthma.

In Part 2, only patients with eosinophilic asthma will be assessed for GLG at 2, 4, and 6 weeks, after randomization to placebo or treatment with a single dose of reslizumab.

In Part 2, the primary efficacy endpoint is the change from baseline to week 4 in GLG (ΔGLG).

The radiology center at [redacted] will determine the following:

GLG is the total FDG uptake in the whole lung.

A region of interest (ROI) is drawn around lung boundary in each axial slice. SUVmean and area of each ROI is recorded. Using the formula: area*slice thickness, the volume of each slice is calculated. Then SUVmean of each slice is multiplied by the volume of the corresponding slice, which will represent the total FDG uptake in one slice. This product for each slice is summed over number of slices to provide GLG of that lung for each subject/patient as follows:

GLG=$\sum_1^n(area * slice\ thickness * SUV\ mean)$

n=number of slices

Intra-subject/patient variability (reproducibility measurement (Part 1) :

Below is the calculation to determine the intra-individual variability between PET/CT scans as measured by GLG for HC subjects and patients with eosinophilic asthma. The accepted variability within each group is ≤10% and will be calculated as follows:

Relative difference of **GLG (HCs) = (GLG2-GLG1)/GLG1** (For HC subjects)

Relative difference of **GLG (patients with eosinophilic asthma) = (GLG4-GLG3)/GLG3** (For patients)

1= First measurement (HCs)

2= Second measurement (HCs)

3= First measurement (patients with eosinophilic asthma)

4= Second measurement (patients with eosinophilic asthma)

A 10% variability (measured as a relative difference between the first measurement and second measurement) between PET/CT scans as measured by GLG within each group (HCs, n=5) and patients (n=10), will be considered as the maximum allowed intra-group variability.

Relative differences between the first (V2) and second (V3) measurements will be summarized, by total/regional lung and patients/HC group, using descriptive summary statistics, based on enrolled analysis set (Summary 15.2.1.1).

Variability between HC group and individual patients with eosinophilic asthma (Part 1):

The planned method to assess whether the difference in GLG measure between HC subjects, as a group, and individual patients (one-by-one) with eosinophilic asthma is ≥5% will be calculated as follows:

- For Females: Relative difference of GLG = (GLG6i-GLG5f)/GLG5f, i.e., difference in GLG (based on average of 2 measurements) between each individual patient with asthma and the mean of HC group, for females.
- For Males: Relative difference of GLG = (GLG6i-GLG5m)/GLG5m, i.e., difference in GLG (based on average of 2 measurements) between each individual patient with asthma and the mean of HC group, for males.

5=average of 2 GLG measurements (1 and 2) of all HCs by sex

6=average 2 GLG measurements (3 and 4) for each individual asthma patients

GLG6i will be calculated for each individual male/female patient using his/her two GLG measurements at V2 and V3 (Part 1). If this amount is ≥ 5% then the patient will be randomized.

Relative differences in GLG measures between the HC group and individual patients with asthma will be summarized for each sex, by total lung/regional lung, using descriptive summary statistics, based on enrolled analysis set (Summaries 15.2.1.2 and 15.2.1.3).

Relative change from baseline to week X in GLG (ΔGLG) (Part 2):

ΔGLG = (GLGwX –GLGbaseline)/GLGbaseline

wX= post-randomization week (week 2 /V5, week 4/V6, and week 6/V7).

GLG Baseline= the average of two measurements at Visits 2 and 3 of Part 1 (see section 4.2 of the SAP).

SUV mean:

SUV is a well validated measure which normalizes FDG uptake by any particular object/tissue volume by the administered dose and either total body weight or total body surface area. Regions of interest (ROIs) will be drawn manually around the outer boundaries of the lung on every transverse slice passing through the lung on fused FDG PET/CT images from each subject. The trachea and main stem bronchi will be excluded from the ROIs to capture only the inflammation in the lung parenchyma. Lung sectional mean standardized uptake value (sSUV mean) and the area of the lung ROI will be recorded from each slice. Subsequently, the sectional lung volume (sLV) will be calculated from each slice by multiplying the lung ROI area (in centimeters squared) by 0.4 (slice thickness 4 mm). The sectional lung glycolysis (sLG) will be determined by multiplying sLV and lung sSUV mean from each slice. The lung volume (LV) will be calculated by adding all the sLV from slices passing through the lung, and the global lung glycolysis (GLG) will be determined by adding all the sLG from slices passing through the lung.

Finally, the lung SUV mean will be calculated as follows:

SUV = GLG/LV.

Similar methodology is applied to lymph nodes and bone marrow. See section 6.4.3 of this SAP.

6.2.2. Primary Efficacy Analysis

For Part 1, intra-group variability and variability between HC group and individual patients with eosinophilic asthma data and all variables which enter into these calculations will be listed.

For Part 2, change in GLG from baseline to each of the postbaseline visits (2, 4, and 6 weeks, after randomization) will be summarized, using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), by treatment group (reslizumab vs placebo) for total and regional lung based on ITT and FAS. The difference in mean changes from baseline between reslizumab and placebo will also be summarized and reported (Summaries 15.2.2.1 to 15.2.2.8).

No inferential statistics will be used for the primary endpoints analyses.

6.2.3. Supportive Primary Efficacy Endpoint Analysis

The supportive primary efficacy endpoint is the change from baseline to week 4 in LP SUVmean (Avg SUVmean).

The same statistical methods used for the analysis of the primary efficacy endpoints of Part 2 above will be used to summarize the supportive primary efficacy endpoints (Summaries 15.2.2.1 to 15.2.2.8).

6.2.4. Sub-Group Analyses

No subgroup analysis will be performed for this study.

6.3. Secondary Efficacy Endpoints and Analysis.

The secondary efficacy endpoints will be descriptively summarized using the same statistical methods used for the primary efficacy endpoint of Part 2 above. In addition, to demonstrate the relationship between the benefit observed on imaging (PET/CT scan) with the secondary endpoints, the correlation between the change from baseline to week 4 for each secondary endpoint and change from baseline to week 4 in GLG (ΔGLG) will be calculated using Spearman's Rho.

No inferential statistics will be used for the secondary endpoints analyses.

6.3.1. Blood Eosinophil Count

6.3.1.1. Definition

The first secondary efficacy endpoint is change from baseline (Day 1/Visit 4) to weeks 2, 4, and 6 in blood eosinophil count.

6.3.1.2. Analysis

Blood eosinophil count value and change from baseline to each of the post-baseline visits (2, 4, and 6 weeks, after randomization) will be descriptively summarized, by treatment group, based on the ITT and FAS. The difference in mean changes from baseline between reslizumab and placebo, and Spearman's Rho will also be summarized and reported (Summaries 15.2.3.1 and 15.2.3.2).

6.3.2. Forced Expiratory Volume (FEV1)

6.3.2.1. Definition

FEV1 will be measured using spirometry. The FEV1 is the volume of air which can be forcibly exhaled from the lungs in the first second, measured in liters.

The second secondary efficacy endpoint is the change from baseline (Day 1/Visit 4) to weeks 2, 4, and 6 in FEV1.

6.3.2.2. Analysis

FEV1 value and change from baseline to each of the post-baseline visits (2, 4, and 6 weeks, after randomization) will be descriptively summarized, by treatment group, based on the ITT and FAS. The difference in mean changes from baseline between reslizumab and placebo, and Spearman's Rho will also be summarized and reported (Summaries 15.2.3.3 and 15.2.3.4).

6.3.3. Fractional Exhaled Nitric Oxide (FeNO) Measurements

6.3.3.1. Definition

The third secondary efficacy endpoint is change from baseline to weeks 2, 4, and 6 in FeNO measurements.

6.3.3.2. Analysis

FeNO measurements and change from baseline to each of the post-baseline visits (2, 4, and 6 weeks, after randomization) will be descriptively summarized, by treatment group, based on the ITT and FAS. The difference in mean changes from baseline between reslizumab and placebo, and Spearman's Rho will also be summarized and reported (Summaries 15.2.3.5 and 15.2.3.6).

6.3.4. AQLQ score

6.3.4.1. Definition

The fourth secondary efficacy endpoint is change from baseline (Day 1/Visit 4) to weeks 2, 4 and 6 in AQLQ.

The AQLQ+12 is a modified version of the standardized self-administered AQLQ questionnaire, which was developed to measure functional impairments experienced by adults ≥17 years of age. The AQLQ+12 is valid for patients aged 12 to 70 years and includes 32 questions/items in 4 domains: asthma symptoms (12 questions: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30), activity limitation by asthma (11 questions: 1 to 5, 11, 19, 25, 28, 31, 32), emotional function (5 questions: 7, 13, 15, 21, 27) and exposure to environmental stimuli (4 questions: 9, 17, 23, 26). Patients are asked to recall their experiences during the previous 2 weeks and score their response options to each of the questions on a 7-point scale where 7 = no impairment and 1 = severe impairment.

The questionnaire is analyzed directly from the scores recorded. First, the overall AQLQ score is calculated as the mean of all 32 responses for each patient and the individual domain scores are the means of the responses within each domain for each patient. For details of the AQLQ+12 questionnaire, see Appendix B of the protocol and Juniper et al (1992).

AQLQ scores were recorded at Visits 4 (Baseline, Day 1), 5, 6 and 7 of Part 2 (see Table 1).

6.3.4.2. Analysis

Mean AQLQ scores and change from baseline to each of the post-baseline visits (2, 4 and 6 weeks after randomization) will be descriptively summarized, for overall score, and each domain, and treatment group, based on the ITT and FAS. The difference in mean changes from baseline between reslizumab and placebo, and Spearman's Rho will also be summarized and reported (Summaries 15.2.3.7 and 15.2.3.8).

6.4. Exploratory Efficacy Endpoints Analysis

No inferential statistics will be used for exploratory efficacy endpoints and analyses.

6.4.1. Biological Markers of Inflammation and Asthma: IgE, DPP4, 25-hydroxy vitamin D, eotaxin-1, -2, and -3, TARC, MCP-1 and MCP-4, ILC2

6.4.1.1. Definition

Blood samples for assessment of biological markers of inflammation and asthma will be collected at Visits 4, 5, 6, and 7 and processed using the procedures in place at the investigational center [redacted]

6.4.1.2. Analysis

Change from baseline (Day 1/Visit 4) to each of the post-baseline visits (2, 4, and 6 weeks after randomization) in biological markers of inflammation and asthma, will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment group, based on FAS. The difference in mean changes from baseline between reslizumab and placebo will also be summarized and reported for each biological marker (Summary 15.2.4.1).

In addition, to explore the relationship between the benefit observed on imaging (PET/CT scan) with the exploratory biomarker endpoints, the correlation between the change from baseline to week 4 for each biomarker endpoint and change from baseline to week 4 in GLG (ΔGLG) will be calculated using Spearman's Rho.

6.4.2. Biological Lung Function Variables: FVC, PEFR, $FEF_{25\%-75\%}$

6.4.2.1. Definition

Forced vital capacity (FVC), PEPR, and $FEF_{25\%-75\%}$ will be measured at baseline (Visit 4) and post-baseline visits 5, 6 and 7, using spirometry (see section 6.2 of the protocol).

The FVC is the volume of air that can be forcibly blown out after full inspiration, measured in liters. The $FEF_{25\%-75\%}$ is the forced expiratory flow at 25% to 75% forced vital capacity. The PEFR is the peak expiratory flow rate, measured in L/min.

Spirometry will be conducted according to American Thoracic Society/European Respiratory Society 2005 procedural guidelines. The National Health and Nutrition Survey III reference equations will be used.

6.4.2.2. Analysis

FVC, PEPR, and $FEF_{25\%-75\%}$ values and change from baseline to each of the post-baseline visits (2, 4, and 6 weeks after randomization) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), by treatment group based on FAS. The difference in mean changes from baseline between reslizumab and placebo will also be summarized and reported for each lung function variable (Summary 15.2.4.2).

In addition, correlation between change from baseline to week 4 in FVC, PEPR, and $FEF_{25\%-75\%}$ and change from baseline to week 4 in GLG (ΔGLG) will be calculated using Spearman's Rho correlation.

6.4.3. Upper-body Uptake of FDG in Lymph Nodes and Bone Marrow

6.4.3.1. Definition

The uptake of FDG in the lymph nodes and bone marrow of the upper body (lower limit of iliac crest) as measured by the PET/CT imaging parameters indicated for the primary efficacy variable (see section 6.1.2 of the protocol and section 6.2.1 of the SAP).

6.4.3.2. Analysis

Change in values of uptake of FDG in the lymph nodes and bone marrow of the upper body from baseline (the average of 2 measurements at V2 and V3 of Part 1) to each of the post-baseline visits (weeks 2, 4, and 6 after randomization) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), by treatment group based on FAS. The difference in mean changes from baseline between reslizumab and placebo will also be summarized and reported for total lymph node inflammation and total bone marrow inflammation (Summary 15.2.4.3).

6.4.4. Sputum Eosinophils

6.4.4.1. Definition

For those patients who can produce sputum, sputum sampling for eosinophils will be performed at Visits 4, 5, 6, and 7.

6.4.4.2. Analysis

Change in values of sputum eosinophils from baseline (Day 1/Visit 4) to each of the post-baseline visits (weeks 2, 4, and 6 after randomization) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), by treatment group based on FAS. The difference in mean changes from baseline between reslizumab and placebo will also be summarized and reported (Summary 15.2.4.4).

In addition, correlation between change from baseline to week 4 in sputum eosinophils and change from baseline to week 4 in GLG (ΔGLG) will be calculated using Spearman's Rho correlation.

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustments will be made for the preplanned multiple comparisons/endpoints.

8. SAFETY ANALYSIS

8.1. General

The safety analyses for Part 2 of the study will be presented by treatment group and overall, based on the safety analysis set.

In addition, safety analysis for Part 1, based on the enrolled analysis set, will be presented by study participants status (HCs vs patients with asthma) and overall.

Combined safety analysis presenting safety data for Part 1 and Part 2 of the study may be provided, as deemed necessary.

Individual listings will also be provided.

8.2. Adverse Events

All adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA), associated with five levels of classifications: a System Organ Class (SOC), a High Level Group Term (HLGT), a High Level Term (HLT), a Preferred Term (PT) and a lowest Level Term (LLT).

Only Treatment Emergent Adverse Event (TEAE), defined as events occurring after the first drug administration and until the end of the study, will be presented, based on Safety analysis set.

Similarly, AEs occurring between ICF signing and end of Part 1 will be presented based on Enrolled analysis set.

In the AE summary tables each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events by treatment group, and overall as following:

- All AEs sorted by SOC and PT based on Safety analysis set (Summary 15.3.1.1) and on Enrolled analysis set (Summary 15.3.1.2)
- All AEs sorted by PT based on Safety analysis set (Summary 15.3.1.3) and on Enrolled analysis set (Summary 15.3.1.4)
- Treatment-related AE sorted by SOC and PT based on Safety analysis set (Summary 15.3.1.5)
- Serious AE sorted by SOC and PT based on Safety analysis set (Summary 15.3.1.6)
- Non serious AE sorted by SOC and PT based on Safety analysis set (Summary 15.3.1.7)
- AE sorted by SOC, PT and severity based on Safety analysis set (Summary 15.3.1.8).

Asthma deterioration will be descriptively summarized for safety analysis set (Summary 15.3.1.9).

Patient listings of serious adverse events and adverse events leading to withdrawal will be presented. Suspected anaphylaxis/hypersensitivity and CPK reactions will be listed individually (Listings 16.2.8.12 and 16.2.8.13).

8.3. Death

If one or more patients die during the study, a listing of deaths will be provided (Listing 16.2.7.4).

8.4. Clinical Laboratory Tests

Laboratory values and changes from baseline (Visit 4 or the last available value pre-dosing study medication) to endpoint (Visit 7) in laboratory test results (in standard international (SI) units)) will be presented, by treatment group and overall, using descriptive summary statistics (n, mean, SD, median, min, max), based on the safety analysis set (Part 2), for serum chemistry (Summary 15.3.2.1), and for serum hematology values and changes from baseline to each post-baseline visit (Summary 15.3.2.2). Urinalysis tests performed at Visits 4 and 7 will be summarized in Summary 15.3.2.3. Specific clinical laboratory tests performed at Screening (Visit 1) and at various visits throughout the study are presented in Table 2 below.

Table 2. Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
β human chorionic gonadotropin (HCG)[a] calcium phosphate sodium potassium chloride creatinine glucose blood urea nitrogen (BUN) cholesterol (low density lipoprotein [LDL]/high density lipoprotein [HDL]/total)[a] triglycerides[a] uric acid alanine aminotransferase (ALT) aspartate aminotransferase (AST) lactate dehydrogenase (LDH) gamma-glutamyl transpeptidase (GGT) alkaline phosphatase bicarbonate or carbon dioxide creatinine phosphokinase total protein albumin total bilirubin direct bilirubin indirect bilirubin	hemoglobin hematocrit red blood cell (RBC) count RBC indices platelet count white blood cell (WBC) count, and differential count and percentage – absolute neutrophil count (ANC) – polymorphonuclear leukocytes (neutrophils) – lymphocytes – eosinophils – monocytes – basophils – atypical lymphocytes – other (to include band granulocytes) international normalized ratio (INR)	B-HCG[a] protein glucose ketones blood (hemoglobin) pH specific gravity microscopic – bacteria – red blood cells (RBCs) – white blood cells (WBCs)

[a] Assessed at the screening visit only.

Shifts (below, within, and above the normal range) from baseline (Visit 4) to each post-baseline visit (hematology) and to endpoint (Visit 7, serum chemistry and urinalysis) will be summarized, by treatment group and overall based on the safety analysis set (Part 2), using patient counts (n) for each serum chemistry lab test (Summary 15.3.2.4), for each hematology lab test (Summary 15.3.2.5), and for each urinalysis lab test (Summary 15.3.2.6).

The incidence of post-baseline (including scheduled, unscheduled, and withdrawal visits) potentially clinically significant abnormal (PCS) abnormal values will be summarized for serum chemistry, hematology and urinalysis laboratory tests (Summaries 15.3.2.7, 15.3.2.8, and 15.3.2.9, respectively), using descriptive statistics (n, %) with the criteria for potentially clinically significant specified in Table 3 below.

Table 3. Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value*
Alanine aminotransferase (ALT)	≥ 3x ULN
Aspartate aminotransferase (AST)	≥ 3x ULN
Alkaline phosphatase	≥ 3x ULN
Gamma-glutamyl transpeptidase (GGT)	≥ 3x ULN
Lactate dehydrogenase (LDH)	≥ 3x ULN
Blood urea nitrogen (BUN)	≥ 10.71 mmol/L
Creatinine	≥ 177 mmol/L
Uric acid Men	≥ 625 mmol/L
Uric acid Women	≥ 506 mmol/L
Bilirubin (total)	≥ 34.2 mmol/L
Hematology	
Hematocrit Men	< 0.37 L/L
Hematocrit Women	< 0.32 L/L
Hemoglobin Men	≤ 115 g/L
Hemoglobin Women	≤ 95 g/L
Hemoglobin Adolescents (12 to 17 years)	≤ 100 g/L
White blood cell (WBC) counts	≤ 3 x 10^9/L ≥ 20 x 10^9/L
Eosinophils	≥ 10%
Absolute neutrophil counts (ANC)	≤ 1 x 10^9/L
Platelet counts	≤ 75 x 10^9/L
	≥ 700 x 10^9/L
Urinalysis	
Blood (HGB)	≥2 unit increase from baseline
Glucose	≥ 2 unit increase from baseline
Ketones	≥ 2 unit increase from baseline
Total protein	≥ 2 unit increase from baseline

* ULN=upper limit of normal range.

For Creatine phosphokinase (CPK) parameter, no PSC will be calculated but the grading scale of the Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials will be used to classify subjects in the four following grades (Summary 15.3.2.9) :

Table 4. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
CPK	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10x ULN	> 10 x ULN

8.4.1. Other Clinical Laboratory Tests

Human chorionic gonadotropin tests (β-HCG) in serum will be performed at screening (Visit 1) only for all participating women of child bearing potential. Urine β-HCG tests will be performed for all participating women of child bearing potential at V2, V3, V4, V5, V6, and V7, before study drug administration and before each PET/CT scan.

Capillary blood glucose will be performed before each PET/CT scan (V2, V3, V5, V6 and V7) to check the glucose level. If a threshold is raised (determined by the investigator), the scan is canceled or postponed. Test results (in standard international (SI) units)) will be presented, by treatment group and overall, using descriptive summary statistics (n, mean, SD, median, min, max), based on the enrolled analysis set (Part 1) and safety analysis set (Part 2).

8.5. Physical Examinations

Complete physical examinations, including height and weight (to be obtained at screening visit only) are to be performed at Visit 1 and Visit 7.

The “full” physical examination should include the following organ systems: General appearance; Head, Eyes, Ears, Nose, and Throat; Chest and Lung; Heart; Abdomen; Musculoskeletal; Skin; Lymph Nodes; and Neurological.

The “brief” physical examination recorded at Visits 4, 5, and 6 (Part 2) only should include at minimum the following organ systems: General appearance; Head, Eyes, Ears, Nose, and Throat; Chest and Lung; and Heart.

Any physical examination finding that is judged by the investigator as clinically significant will be considered as an adverse event, recorded on the CRF in the same way and will then be displayed with AEs (Summaries 15.3.1).

Newly occurring abnormalities in the physical examinations will be identified and listed.

Only percentages of subjects with physical abnormalities will be displayed in the safety part (Summary 15.3.4.1).

8.6. Vital Signs

Vital signs (blood pressure, respiratory rate, body temperature, pulse, and blood oxygen saturation (SpO2) will be measured at Screening (Visit 1) and at Visits 4, 5, 6 and 7. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any abnormal vital sign value that is judged by the investigator as clinically significant will be recorded on the source documentation, transcribed to the CRF as an adverse event.

Summary statistics for vital signs: blood pressure, respiratory rate, body temperature, pulse, and SpO_2 will be presented at baseline (visit 4), visit 5, visit 6 and visit 7 and will include:

- Vital signs values and changes from baseline (Visit 4) to each post-baseline visit will be summarized, by treatment group, based on the safety analysis set, using descriptive statistics (Summary 15.3.3.1). Individual listings will also be provided.
- Summaries of potentially clinically significant (PCS) abnormal values will include all post-baseline values (including scheduled, unscheduled, and withdrawal visits). The incidence of potentially clinically significant abnormal values will be summarized (Summary 15.3.3.2) using descriptive statistics (n, %) with the criteria for potential clinical significance abnormal values specified in Table 5 below.

Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: i.e., have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column.

Table 5. Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	>100 bpm	Increase of ≥30
	<50 bpm	Decrease of ≥30
Systolic blood pressure	>160 mm Hg	Increase of ≥30
	<90 mm Hg	Decrease of ≥30
Diastolic blood pressure	>100 mm Hg	Increase of ≥12
	<50 mm Hg	Decrease of ≥12
Respiratory rate	>24 breaths/min	Increase of ≥10
	<6 breaths/min	Not applicable
Temperature	<96.5°Fahrenheit	Not applicable
	>100.5°Fahrenheit	Increase of ≥2
SpO2	pulse oximeter <88%	

8.7. Electrocardiography

Any abnormal ECG value that is judged by the investigator at the screening visit (or at unscheduled visit if applicable) as clinically significant will be recorded as an adverse event.

The incidence of patients meeting PCS thresholds for each QT_c Bazett and Fridericia interval will be summarized (Summary 15.3.X.X) using descriptive statistics (n, %).

The predefined threshold values for absolute QTc Bazett and Fridericia interval prolongations at baseline are > 450 msec and > 500 msec.

8.8. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Details of prohibited medications can be found in Section 5.3 of the study protocol. All concomitant medications will be coded using the latest version of the WHO Drug dictionary.

The incidence of prior medications taken prior to study drug administration at Baseline (Visit 4) and reported at Visit 2 and 3 will be summarized using descriptive statistics (n,%), sorted by therapeutic class category and preferred term, according participant/treatment group based on enrolled analysis set (Summary 15.3.6.1) and on safety analysis set (Summary 15.3.6.2).

The incidence of concomitant medications i.e., medications taken after the study drug administration at baseline during Part 2, will be summarized, by treatment group based on safety analysis set (Summary 15.3.6.3).

Patients/subjects are counted only once in each therapeutic class, and only once in each preferred term category.

9. TOLERABILITY VARIABLES AND ANALYSIS

Since this is a single-dose study, Tolerability was not specifically defined for this study.

10. IMMUNOGENICITY ANALYSIS

ADA blood samples for serum ADA assay will be obtained at baseline before study drug administration (Visit 4) and at Visits 5, 7 and at possible unscheduled visits. Descriptive summary statistics will be provided using descriptive analysis (n, %) for each visit, indicated if tests are positive or negative at each timepoint (Summary 15.3.7.1). Samples from placebo-treated patients will not be analyzed. See section 1.3 of the SAP.

11. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

12. REFERENCES

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