Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan

Title	:	Reporting and Analysis Plan for 450 Participant/6 Month Strategic Interim and Final Analysis for Study 205724: Randomized, Double-Blind (Sponsor Open), Placebo-Controlled, Multi-centre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared with Placebo for 24 Weeks in Adult Participants with Chronic Obstructive Pulmonary Disease
Compound Number	:	GSK1325756
Effective Date	:	30-OCT-2018

Description:

- The purpose of this Reporting and Analysis Plan is to describe the planned 450 participant/6 month strategic interim and final analyses and output to be included in the Clinical Study Report for Protocol 205724.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the 450 participant/6 month strategic interim. This RAP will also describe the final analyses to be included in the Clinical Study Report (CSR) for Protocol 205724.

Revision Chronology:		
2016N293867_00	28-NOV-2016	Original
2016N293867_01	31-OCT-2017	• Adds a second, optional, detailed pharmacokinetic profiling at Visit 10 in a subset of participants to allow for a better understanding of danirixin pharmacokinetics. • Removes the Participant Exit Interview from the exploratory endpoints. • Provides additional information and clarification for the following: spirometry assessments, exclusion for cancers other than lung cancer, permitted use of supplemental oxygen, permitted uses of chronic steroids, participant numbering requirement for rescreening, additional text to explain the timing of the planned interim analysis and updates to the analysis populations.

1.1. RAP Amendment

Revision chronology:

RAP Section	Amendment Details
GSK1325756-205724 Statistical Analysis Plan Reporting and Analysis Plan Version 001 (31-Aug-2018)	
GSK1325756-205724 Reporting and Analysis Plan Amendment1_Final [Insert Date]	
Approvals	• Removed PPD as she has left GSK. Added PPD PPD replacement) as an additional approver
2.2 Study Objectives and Endpoints	• PK endpoints were not assessed in the strategic interim
3.1.3 Strategic Analysis	• Updated to past tense
3.2 Final Analysis	• Updated to reflect planned unblinding process
4.1 Strategic Interim Analysis, 7.1.4.5.1 Bayesian MMRM Methodology Specification and 7.2.1.5.1 Statistical Methodology Specification	• ITT and Symptomatic populations not used for final analysis. • (PP) added to Per Protocol population in the definition table.
6.1.2 Prior and Concomitant Medications	• Additional concomitant medication table at Month 6
7.1.1 Month 6 E-RS: COPD Total Score Dose-Response Analysis	• Clarification of posterior predictive probability of success calculation used at the Strategic Interim

RAP Section	Amendment Details
7.1.2 Month 2-6 E-RS: COPD Total Score Dose-Response Analysis and 7.1.3.5.2 Frequentist ANCOVA Methodology Specification and 14.6.3 Efficacy	• Month 2-6 E:RS: COPD Dose Response Analysis not required
7.1.4.5.1 Bayesian MMRM Methodology Specification	• Updates to Bayesian model specifications to improve convergence and mixing
7.1.4.5.3 Frequentist MMRM Methodology Specification	• Additional plots of LS Mean and daily mean E-RS: COPD scores. Plots of empirical distribution function for E-RS: COPD Total Scores.
7.2.1.5.1 Statistical Methodology Specification	• Additional table for HCRU exacerbations treated with antibiotics.
7.2.4 SGRQ Total Score and CAT Score	• Additional plot of arithmetic mean and 90% CIs for SGRQ and CAT
7.2.5 Rescue Medication	• Additional plots daily rescue medication use
7.3.1 E-RS: COPD Total Score	• Identify subgroups not required for final SAC
7.3.3 Time to First Clinically Important Deterioration	•
8.3 Clinical Laboratory Analysis	• Remove urinalysis outputs because no PCI ranges are defined for urinalysis
8.4.5.1 Frequentist MMRM Methodology Specification	• Additional summaries of FEV1/FVC ratio and plots of arithmetic mean and 90% CIs for all spirometry endpoints.
11 Biomarker Analysis	• Additional tables and boxplots in subjects with pneumonia
14.4.1.1 Study Phases for Diary Data	• Clarify that Diary data phases applies to EXACT events
14.6.2 Study Population	• Additional COPD medication combinations table at Month 6
14.6.3 Efficacy	• Clarify definitions for Season, time to first, raw annual rate and offset. Remove definition of CID as not reporting this exploratory endpoint.
14.6.4 Safety	• Clarify definition for character laboratory parameters. Add definition of ICS use for pneumonia table.
14.11 Appendix 11: List of Data Displays	• Updates to tables and figures. • Remove urinalysis outputs • Remove CID tables

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• All Participants population	• All Subjects population	• R&D Clinical Data Standards Board (CDSB) recommendation to use the term 'Subjects' in all displays (Tables, Figures & Listings)
• No Intent-to-treat (ITT) population	• ITT population defined to be used for selected efficacy displays	• Used for key efficacy displays to enable phase III planning
• No Per Protocol (PP) population	• PP population defined and used for efficacy displays	• Remove data from participants who had a protocol deviation considered to impact efficacy during the treatment period.
• No Symptomatic population	• Symptomatic population defined and used for selected study population and efficacy displays	• Used to explore the subgroup of symptomatic participants.
• No PK2 population	• PK2 population defined and used for PK dry blood spot vs wet whole blood	• Used to compare dry blood spot with wet whole blood
• mITT population used for efficacy endpoints	• PP population used for efficacy endpoints	• Remove data from participants who had a protocol deviation considered to impact efficacy during the treatment period.
• The final Emax model will be repeated using months 1-6 and months 3-6.	• The final Emax model will be repeated using months 2-6.	• Team decision to include most informative time period.
• The protocol states that exacerbation rates for the danirixin and placebo groups, along with the ratio in exacerbation rates danirixin/placebo, will be estimated and corresponding 95% credible intervals will be produced.	• 90% credible intervals will be produced for all Bayesian efficacy analyses including exacerbation rates.	• Inconsistency in protocol.

2.2. Study Objectives and Endpoints

Objectives	Endpoints	Assessed in Strategic Interim
Primary Objectives	**Primary Endpoints**	
• To characterize the dose response of danirixin compared with placebo on the incidence and severity of respiratory symptoms in participants with chronic obstructive pulmonary disease (COPD)	• Change from baseline in respiratory symptoms measured by the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) daily diary: total score and subscales (i.e. breathlessness, cough and sputum, and chest symptoms)	Yes
• To compare the safety of danirixin with placebo in participants with COPD	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG)	Yes[1]
Secondary Objectives	**Secondary Endpoints**	
• To characterize the dose response of danirixin compared with placebo on the annual rate of moderate/severe COPD exacerbations in participants with COPD	• Healthcare Resource Utilization (HCRU)-defined COPD exacerbations	Yes
• To further characterize the clinical activity of danirixin compared to placebo in participants with COPD	• E-RS: COPD Responder Analysis (including subscales)	Yes
	• Number of Exacerbations of Chronic Pulmonary Disease (EXACT) tool defined events	No
	• Time to first EXACT event	No
	• EXACT event severity	No
	• EXACT event duration for all events	No
	• Time to first HCRU-defined COPD exacerbation	Yes
	• Time to first severe HCRU-defined COPD exacerbation	Yes
	• HCRU-defined COPD exacerbation duration	Yes
	• Change from baseline for the St. George's Respiratory Questionnaire (SGRQ) total score (derived from	Yes

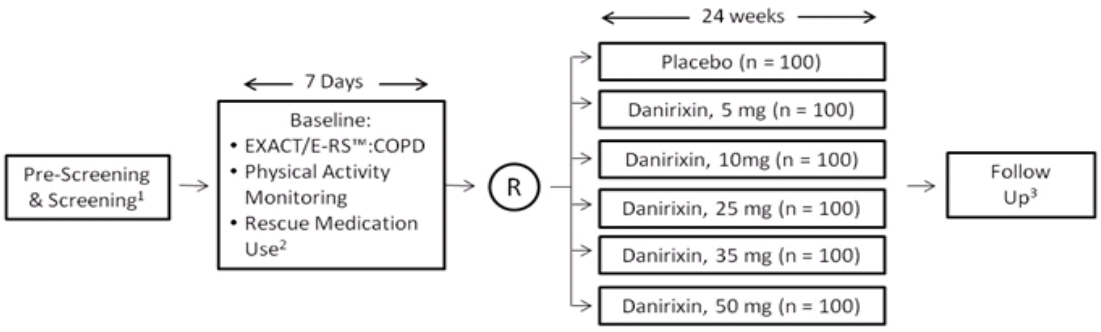
Objectives	Endpoints	Assessed in Strategic Interim
	SGRQ-C)	
	• SGRQ responder analysis	Yes
	• Change from baseline for the COPD Assessment Test (CAT) total score	Yes
	• CAT responder analysis	Yes
	• Lung function (forced expiratory volume in 1 second [FEV1], FEV1 % predicted, forced vital capacity [FVC], FEV1/FVC ratio)	Yes
	• Rescue medication use	Yes
	• Participant experience of physical activity (subset of approximately 50% of participants) measured using Clinical Visit PROactive Physical Activity in COPD Tool (C-PPAC)	Yes[2]
• To characterize the pharmacokinetics of danirixin in participants with COPD	• Danirixin concentration and standard pharmacokinetic (PK) parameters for danirixin (e.g. AUC, Cmax, Tmax), using dried blood spot data	No
Exploratory Objectives	**Exploratory Endpoints**	
• To further explore study participants' experience with study treatment and overall experience with the study	• Time to first Clinically Important Deterioration (CID)	No
	• SGRQ domains	Yes
• To characterize the effect of danirixin on lung matrix destruction/remodelling	• Blood/serum/plasma biomarkers that are indicative of extracellular matrix turnover/remodelling (e.g. elastin and collagen neo-epitopes)	No
• Comparison between dried blood spot and wet whole blood analysis of danirixin concentrations in partipants with COPD	• Danirixin concentration and standard pharmacokinetic parameters for danirixin (e.g. AUC, Cmax, Tmax)	No

Objectives	Endpoints	Assessed in Strategic Interim
• To characterise danirixin exposure-response relationships for various safety parameters, if appropriate	• Danirixin systemic exposure and various efficacy/pharmacodynamic (PD)/safety parameters, if appropriate	No

[1] AEs, serious AEs (SAEs), drug-related AEs, AEs leading to withdrawal, AEs of special interest (AESI), laboratory data, ECG
[2] Summary of C-PPAC questionnaire responses only

2.3. Study Design

Overview of Study Design and Key Features



[1]Up to 30 Days Before Visit 2 (i.e. up to 30 days prior to start of baseline assessments)

[2]Rescue Medication Baseline use to include MDI sensor and daily diary

[3]Follow up visit to occur within 28 days of last dose of study treatment

Design Features	This is a parallel group, randomized, double-blind (sponsor open), placebo-controlled, multi-centre, dose ranging study.
Dosing	Study treatment will be administered twice daily for 24 weeks.
Time & Events	Refer to Appendix 2: Schedule of Activities
Treatment Assignment	Participants will be randomized (1:1:1:1:1:1) to receive one of five dose strengths of danirixin (5 mg, 10 mg, 25 mg, 35 mg and 50 mg) or placebo. Randomization was stratified by smoking status.
Interim Analysis	Three specific interim analyses were defined for the study, with the protocol allowing for additional administrative interims as required. An administrative interim was performed in October 2017 and included plots of E-RS: COPD total score (and subscale scores) over time by treatment, to aid internal decision-making on the project. The first protocol specified interim analysis was an evaluation of danirixin PK after 10 participants in each treatment group had completed Visit 3

Overview of Study Design and Key Features	
	(Day 1). This analysis was performed in December 2017. A protocol specified futility interim analysis based on the E-RS: COPD endpoint was conducted after approximately 150 participants had completed 3 months of study treatment. This analysis was performed in February 2018. A further protocol specified strategic interim analysis will be conducted when approximately 450 participants have completed 6 months of treatment. This strategic interim will be used to support GlaxoSmithKline (GSK) decisions regarding additional investment and further development of danirixin. It will include endpoints as specified in Section 2.2 and in the list of data displays in Appendix 11. No changes will be made to the study based on the results of this strategic interim analysis unless a safety concern is identified. Outputs containing unblinded treatment assignments will be created for all interim analyses and will only be made available to a limited number of GSK staff. Full details will be included in the study results dissemination plan (SRDP).

2.4. Statistical Hypotheses

The primary efficacy endpoint is the change from baseline of E-RS: COPD total score at Month 6. The primary objective of the study is to characterize the dose response of danirixin and select appropriate dose(s) for future drug development.

A model based probability inference approach in Bayesian framework will be used to guide decision-making around dose selection. The posterior probability that the change from baseline of E-RS: COPD total score for each active dose is less than placebo will be derived.

No formal statistical hypothesis will be tested in the primary efficacy analysis.

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Interim PK Analysis

After approximately 10 participants in the PK subset for each treatment group had completed Visit 3 (Day 1), an interim evaluation of danirixin PK parameters was undertaken. The purpose of the interim PK analysis was to determine if danirixin exposures were within the expected range. No formal HARP outputs were produced.

3.1.2. Futility Analysis

An interim analysis was conducted to allow for the possibility of stopping early for futility after approximately 150 participants had completed 3 months of treatment. This is described in a separate RAP. Outputs featuring unblinded treatment assignments were created and shared with the study team and those listed in the Study Results Dissemination Plan (SRDP).

3.1.3. Strategic Analysis

When approximately 450 participants had completed 6 months of treatment, a further interim analysis was performed for strategic planning purposes, as described in this RAP. This analysis was planned to be used to aid in the planning of future studies and for a better understanding of benefit/risk profile of danirixin. No changes were made to the study based on the results of this strategic interim analysis.

The analyses were performed after the completion of the following sequential steps:

1. The date of the planned Visit 10 for the 450th completed participant (01AUG2018) had been met.
2. All required database cleaning activities had been completed by Data Management (DM) on data collected up until 01AUG18. Data collected between 02AUG2018 and 5SEP2018 (DBR) for ongoing subjects was not cleaned.
3. Unblinded randomization schedules were released by Randomization coordinator.

Data was reported in System Independent (SI) format. Outputs featuring unblinded treatment assignments were created for this strategic interim analysis, reviewed by the study team and shared with selective GSK personnel (to be included in the SRDP).

3.1.4. Administrative Interims

Administrative assessments of danirixin exposure, efficacy and spirometry data may be undertaken during the conduct of the study as data becomes available. No decisions regarding study conduct will be made based on these assessments. The reporting team will have access to the unblinded participant treatment assignments. The unblinded study team (as defined in the 205724 Study Charter) will have access to unblinded aggregate data grouped by study treatment assignment.

An administrative interim was performed in October 2017 and included plots of E-RS: COPD total score (and the subgroups) over time by treatment, to aid internal decision-making on the project.

3.2. Final Analyses

The final planned analyses for this Clinical Data Interchange Standards Consortium (CDISC) study will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. SI data to Study Data Tabulation Model (SDTM) data conversion has been completed by Accenture and quality control (QC) of blinded SDTM has been completed by CDAD and DM. DM will provide the blinded SI PC dataset to Accenture.
3. All required database cleaning activities have been completed and final SI Source Data Lock (SDL) has been declared by DM.
4. Study is unblinded
    - Randomization schedules and container data are released in RANDALL NG.
    - SMS2000 data is released in HARP
5. The SDTMs (including the PK) are unblinded by clinical programming (or representative) using the interim unblinding process.
6. Database freeze (DBF) on unblinded SDTM datasets is declared by DM.

4. ANALYSIS POPULATIONS

4.1. Strategic Interim Analysis

Population	Definition / Criteria	Analyses Evaluated
All Subjects (ALLSUB)	• All participants screened and for whom a record exists on the study database.	• Participant disposition • Reasons for withdrawal prior to randomization • Inclusion/exclusion/randomization criteria deviations for non-randomized participants • AEs and SAEs for non-randomized participants
Intent-to-treat (ITT)	• All randomized participants apart from those who were randomized in error (i.e. were also recorded as screen or run-in failures and did not receive a dose of study treatment). • Any participant who receives a treatment randomization number will be considered to have been randomized. • Randomized participants will be assumed to have received study medication unless definitive evidence to the contrary exists. • Data will be reported according to the randomized treatment.	• Selected efficacy displays as described in Section 7 • Strategic Interim only
Modified Intent-To-Treat (mITT)	• Same as the Intent-to-treat population, but this population will be 'modified' in that all data summaries and analyses for this population will be based on the actual treatment received, if it is different to the randomized treatment. • If any participant received more than one treatment during a treatment period, their data will be reported according to the treatment they received for the longest period of time.	• Study Population • Safety
Per Protocol (PP)	• All participants from the mITT population who did not have a protocol deviation considered to impact efficacy	• Efficacy
Symptomatic	• All participants in the PP population who have Chronic Mucus Hypersecretion (CMH) according to baseline SGRQ (see Section 14.6.2) and baseline E-RS: COPD total score (see Section 5.2) >=10.	• Study Population • Selected efficacy displays as described in Section 7 • Strategic Interim only

Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.2. Final Analysis

The final analysis will use the same populations as above, plus additional populations as defined below.

Population	Definition / Criteria	Analyses Evaluated
PK	• All participants in the mITT population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values) obtained and analysed whilst on treatment with danirixin.	• PK
PK2	• All participants in the PK population who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values) obtained and analysed whilst on treatment with danirixin from a dry blood spot sample and corresponding wet whole blood sample.	• PK Dry Blood Spot vs Wet Whole Blood

Refer to Appendix 11: List of Data Displays which details the population used for each display.

In the event one or more investigators are withdrawn from the study due to concerns over protocol deviation then a further population will be defined which will consist of all participants in the PP population excluding participants from those investigative sites. This population will be used to perform additional sensitivity analysis for the primary efficacy endpoint only and will only be defined if the combined enrolment at these sites exceeds ≥ 2% of the overall PP study enrolment. No other analyses will be repeated.

4.3. Protocol Deviations

Protocol Deviations (PDs) will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (6JUL2018, V2.0):

- Data will be reviewed prior to SDL to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- Participants who received an incorrect treatment container will be captured as an important protocol deviation. Whether or not the incorrect container contained incorrect treatment will be identified following DBF in the analysis dataset and the PD will be flagged accordingly.
- This dataset will be the basis for the summaries and listings of protocol deviations.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarised and listed.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
D5	Danirixin 5mg	DNX 5mg	2
D10	Danirixin 10mg	DNX 10mg	3
D25	Danirixin 25mg	DNX 25mg	4
D35	Danirixin 35mg	DNX 35mg	5
D50	Danirixin 50mg	DNX 50mg	6
PO	Placebo oval	Placebo	1
PR	Placebo round	Placebo	1

Treatment comparisons will be displayed as in the danirixin dose column with the descriptor: Column vs Placebo.

5.2. Baseline Definitions

Any assessments made after the start of study treatment will not be included in the derivation of baseline. Assessments made on the same day as the start of treatment are assumed to be taken prior to first dose.

If baseline data are missing, no derivation will be performed and baseline will be set to missing.

Parameter	Baseline Used in Data Display
E-RS: COPD total and subscale scores	Mean score during a stable period between (Latest of (7 days before Study treatment start date (Day 1) and day of Visit 1 (Screening)) and day before Day 1 of study treatment. Data must be present on at least 4 days
EXACT (for determining EXACT events)	Defined according to the EXACT User Manual v8.0 (Evidera, 2016a)
SGRQ total and domain scores	Day 1
CAT score	Day 1
Rescue use (diary card and sensor data, mean number of puffs/occasions per day and percentage of rescue-free days)	Mean score during a stable period between (Latest of (7 days before Study treatment start date (Day 1) and day of Visit 1 (Screening)) and day before Day 1 of study treatment. Data must be present on at least 4 days.
PROactive score	A PROactive Total Score and two domain scores (amount and difficulty) will be derived using data from the C-PPAC questionnaire on Day 1 and physical activity

Parameter	Baseline Used in Data Display
	monitor worn between Visit 2 and Visit 3 (7 days). The activity monitor must have been worn for at least 3 days with >=8 hours wearing (the 3 days do not need to be consecutive). Further details of the derivation are described in Section 14.6.3 and in the IMI PROactive user manual (14JUN16).
Blood pressure (BP)	Latest pre-dose assessment with a non-missing value for both systolic and diastolic BP, including those from unscheduled visits
Pulse rate, laboratory data, ECG	Latest pre-dose assessment with a non-missing value for the individual assessment, including those from unscheduled visits
Post-bronchodilator (BD) FEV1, post-BD FVC	Day 1

5.3. Multicentre Studies

In this multicentre global study, enrolment will be summarized by country and investigative site. Country will be included as a fixed effect in statistical models and treatment by country interaction investigated as described in Section 7 and Section 8. Results will be presented for all countries combined except as specified in Section 7.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The covariates and other strata listed below will be used in statistical models and treatment by covariate/stratum investigated as defined in Section 7, Section 14.6.2 and Section 14.6.3.

Category	Details
Strata	Smoking status
Covariates	Treatment, visit/Month, baseline, smoking status at screening, country, gender, exacerbation history (≤1, ≥2 moderate/severe), post-bronchodilator % predicted FEV1, CMH status at baseline, season of data collection.

5.4.2. Examination of Subgroups

The subgroups listed below will be used in statistical analyses as described in Section 7.

Subgroup	Categories
Season	Spring, Summer, Fall, Winter (see Section 14.6.3)
Country	Australia, Canada, Germany, Korea, Netherlands, Poland, Romania, Spain, US
Exacerbation history	History of ≥2 moderate/severe exacerbations vs <2 moderate/severe exacerbation
COPD medication at Baseline	ICS+LABA+LAMA vs. ICS+LABA vs. LABA+LAMA vs. Other COPD medication
ERS10	Baseline E-RS: COPD Total Score <10, ≥10
CAT10	Baseline CAT Score <10, ≥10
Smoking status at Screening	Current, Former
% predicted FEV1 at Screening	<50%, ≥50%
CMH status at baseline	CMH+, CMH- (see Section 14.6.2)

5.5. Multiple Comparisons and Multiplicity

No multiplicity adjustment will be made for this study, as the primary objective of the study is to model the danirixin dose response and use it to select Phase III dose(s).

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

Study population displays including analyses of participant disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Results will be presented for each treatment and overall.

Details of the planned displays including the population to be used for each display and which displays are produced for the strategic interim are presented in Appendix 11. Additional details are provided below.

6.1.1. Demographic and Baseline Characteristics

The summary of exacerbation history at Screening will include the number and percentage of participants reporting mild, moderate, severe and moderate/severe exacerbations (0, 1, >=2; see Section 14.6.2) in the 12 months prior to screening.

6.1.2. Prior and Concomitant Medications

Non-COPD medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 classification and ingredient. Multi-ingredient non-COPD medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

COPD medication tables will report by respiratory medication class (RMC) and ingredient (See Section 14.6.2). The number and percentage of participants taking each medication in the RMC categories (defined in Section 14.6.2) will be presented.

The number and percentage of subjects taking each medication in the RMC categories ICS, LABA, LAMA, PDE4 inhibitors, Xanthines, Anti-IgE, Anti-IL5 and combinations of these RMCs on the day of the Screening visit, at Baseline (Day 1) and at Month 6 will be presented.

6.1.3. Exposure and Treatment Compliance

Calculation of treatment compliance will be based on the number of tablets dispensed and returned as described in Section 14.6.2. Calculation of diary compliance will be based on the number of days with non-missing E-RS: COPD total score as described in Section 14.6.2. Percentage treatment and diary compliance will be summarized categorically and with descriptive statistics.

7. EFFICACY ANALYSES

Details of the planned displays including the population to be used for each display and which displays are produced for the strategic interim are presented in Appendix 11. Additional details are provided below.

For this study, no data were scheduled to be collected after discontinuation of study treatment, therefore accounting for non-recorded missing data following study withdrawal is addressed by the strategy for the intercurrent event of treatment discontinuation.

7.1. Primary Efficacy Analyses

7.1.1. Month 6 E-RS: COPD Total Score Dose-Response Analysis

The estimand is the effect of actual treatment in the population of participants who did not experience a protocol deviation considered to impact efficacy and completed six months of treatment.

A Bayesian dose response model will be applied to the change from baseline to Month 6 and used to estimate the treatment difference between placebo and each dose.

The dose-response model will be fitted using Bayesian techniques with non-informative priors for E0 and Emax and a functional uniform prior (FUP) for ED50 and the slope parameter, m (Bornkamp, 2014). The rationale for this choice of inference is that the FUP shrinks the dose-response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relationship compared to maximum likelihood.

For the strategic interim, the posterior predictive probability of success (PPS) at the end of the study will be calculated for each dose using the formula suggested by Spiegelhalter et al. (Spiegelhalter, 2004) as follows:

$$PPS = \Phi\left[\frac{\sqrt{(m+n)}}{\sqrt{mn}}\frac{(-my_m)}{\sigma_{trt\ diff}} + \sqrt{\frac{m}{n}}z_{0.9}\right]$$

Where m is the average number of participants with Month 6 data in the placebo and comparative dose arm, n is the average number of participants yet to be observed (assuming 90% of participants, rounded to the nearest integer, in each treatment group will provide month 6 data at end of study. If the actual number of participants at month 6 exceeds this, the actual number will be used), y_m is the posterior mean difference from the fitted model, and $\sigma_{trt\ diff}$ is the standard deviation (SD) of the posterior mean difference.

7.1.1.1. Endpoint

Change from baseline in Month 6 E-RS: COPD total score as defined in Section 14.6.3.

7.1.1.2. Summary Measure

For the strategic interim, the summary measure is the posterior predictive probability of success for each danirixin dose, where success is the probability that a true difference from placebo is less than 0 is >95% at Month 6.

For the final analysis, the summary measure is the posterior probability that a true difference from placebo is less than 0 at Month 6 for each danirixin dose.

7.1.1.3. Population of Interest

PP population.

7.1.1.4. Strategy for Intercurrent (Post-Randomization) Events

For the primary efficacy analysis, the intercurrent event of interest is occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1). An 'as treated' strategy will be used to account for this event - only Month 6 E-RS: COPD data (see Section 14.6.3) collected prior to the occurrence of a protocol deviation considered to impact efficacy will be used in the analysis.

The intercurrent event of treatment discontinuation is accounted for in the endpoint definition as only data at Month 6 will be used.

7.1.1.5. Statistical Analyses / Methods

7.1.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in Month 6 E-RS: COPD total score
Model Specification
Bayesian dose response model: • Models of the following form will be considered: Response=E0+ Emax* f(dose) ○ Log-linear model: f(dose)=log(dose+0.01), where 0.01 is an offset to allow the model to fit for zero dose (placebo). ○ 3-parameter emax model: f(dose)=dose/(dose+ed50) ○ 4-parameter emax model: f(dose)=dose^m/(dose^m+ED50^m) Where: ○ E0 = the response at dose = 0 (placebo), ○ Emax = the maximal response over placebo, ○ ED50= the dose that yields 50% of the maximal response, ○ m= dose-response slope parameter. • The log-linear, 3-parameter emax and 4-parameter emax model will be fitted without adjusting for covariates. If possible, covariates (i.e., baseline, smoking status, country) will be included in the E0 and Emax terms of the model for the final analysis • Normal non-informative priors will be used for the E0 and Emax parameters with mean 0 and SD 100. A FUP will be used for the ED50 and m parameters (Bornkamp, 2014), where the

prior density for the FUP is based on all the parameters in the model. An inverse -gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance.

- Parameters will be blocked such that the MCMC procedure samples from E0 and Emax first, then the ED50 and m parameters and then finally the residual variance parameter.
- For the functional uniform priors, the density will be calculated for values of dose from 0.0001 to 50 in steps of 5 (i.e. 0.0001, 5.0001, 10.0001,…, 50.0001).
- 3 MCMC chains will be fitted using the following starting values (as required for the parameters in each particular model):

Parameter	Chain 1	Chain 2	Chain 3
E0	Posterior mean for placebo from MMRM at Month 6 (See Section 7.1.3)	-15	15
Emax	Posterior mean for 50mg dose from MMRM at Month 6 (See Section 7.1.3)	15	-15
ED50	25	10	50
M	1	2	4
Residual variance	6	8	10

- 100,000 MCMC samples will be generated using a thin of 50 to leave 2000 retained samples, and after a burn-in of 10,000 samples for each of the three sets of starting values. All post-burn-in samples from the 3 chains will be used for inference. The number of samples generated and the thin may be increased to reduce the ratio of the MCSE to the posterior SD, as deemed necessary.
- The seeds used to for the three chains were generated using the ranuni function in SAS and are listed in Section 14.5.2.
- The best fitting model will be the model with the smallest average DIC over the 3 chains where convergence is deemed to have been achieved. If the best fitting model is one that adjusts for covariates, all outputs will be presented adjusting for the mean in the observed covariate.
- Production and QC will be deemed to have agreement if the QC value is the following range:
  - if a number is reported to 0dp and there is a difference of $\pm$ 1 (number of participants must agree)
  - if a number is reported to 1dp and there is a difference of $\pm$ 0.1
  - if a number is reported to 2dp and there is a difference of $\pm$ 0.01
  - if a number is reported to 3dp and there is a difference of $\pm$ 0.001
  - if a number is reported to 4dp and there is a difference of $\pm$ 0.0001

Model Checking & Diagnostics

- Posterior density plots and plots of the posterior samples (chains) will be produced for all the parameters in the model.
- The posterior density for the adjusted mean change from baseline in E-RS: COPD total score in each treatment group and differences versus placebo for each danirixin dose will be plotted.
- The Gelman-Rubin R estimate from the three chains will be calculated for all parameters in the model and the differences from placebo for each danirixin dose.

Model Results Presentation

The following will be presented for each analysis based on the best fitting model using all post-burn in samples available.

- The posterior mean, median, SD and 90% credible interval (CrI) for the change from baseline in E-RS: COPD total score for each treatment group.
- The posterior mean and 90% CrI for the difference from placebo for each danirixin dose.

• The posterior probability that difference from placebo is less than 0, -0.5, -1, -1.5 and -2 for each danirixin dose. • For the strategic interim, the posterior predictive probability of success for each danirixin dose, where success is the probability that the difference from placebo is less than 0 is >95%. • A figure of the fitted mean dose response model with the 90% CrI for all possible doses in the dose range, overlaid with the Month 6 adjusted posterior means and 90% CrI from the longitudinal model in Section 7.1.3.
Sensitivity and Supportive Analyses
• At the strategic interim, a supportive analysis will be conducted to estimate the effect of actual treatment in the population of participants who were confirmed as having CMH according to SGRQ, were symptomatic at baseline, did not experience a protocol deviation considered to impact efficacy, and completed six months of treatment. The population used will be the Symptomatic population; all other details will be the same as for the primary analysis.

7.1.2. E-RS: COPD Subscale Scores Dose-Response Analysis

The primary analysis described in Section 7.1.1 will be repeated for the three E-RS: COPD subscale scores of breathlessness, cough and sputum and chest symptoms.

7.1.3. E-RS: COPD Total and Subscale Scores Longitudinal Analysis

The estimand is the effect of actual treatment in the population of participants who did not experience a protocol deviation considered to impact efficacy. A supportive analysis will be performed to assess the effect of randomized treatment in all randomized and dosed participants.

A Bayesian mixed effects analysis with repeated measures (MMRM) will be performed on the monthly E-RS: COPD total and subscale scores.

A frequentist MMRM analysis will be performed on the monthly E-RS: COPD total scores and repeated to assess the impact of various covariates.

7.1.3.1. Endpoint

Change from baseline in monthly mean E-RS: COPD total and subscale scores as defined in Section 14.6.3.

7.1.3.2. Summary Measure

For the Bayesian MMRM the summary measure is the adjusted posterior mean difference from placebo for each danirixin dose.

For the frequentist MMRM the summary measure is the adjusted mean difference from placebo for each danirixin dose.

7.1.3.3. Population of Interest

PP population.

7.1.3.4. Strategy for Intercurrent (Post-Randomization) Events

A 'hypothetical' strategy will be used to account for the intercurrent events of occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1) and treatment discontinuation, to estimate the effect if participants had not deviated from the protocol and remained on treatment. Only E-RS: COPD data prior to the occurrence of a protocol deviation considered to impact efficacy or treatment discontinuation will be used in the analysis. Subsequent data up to Month 6 will be assumed to be missing at random (MAR).

7.1.3.5. Statistical Analyses / Methods

7.1.3.5.1. Bayesian MMRM Methodology Specification

Endpoint / Variables
• Change from baseline in monthly E-RS: COPD total and subscale scores
Model Specification

• Bayesian mixed models repeated measures approach.
• The model will include treatment*visit, baseline*visit, country and smoking status parameters. Note that the model will not include an intercept. Visit will consist of six levels (Month 1-Month 6), and Treatment will consist of six levels (placebo and 5 active doses). If the model does not run, the country covariate will be removed.
• The priors for the mean vector for each of the parameters (i.e covariates) will each follow a normal distribution with mean 0 and SD 1000. The prior for the variance-covariance will follow an inverse Wishart distribution with degrees of freedom equal to the number of visits and an identity scale array. 150,000 samples will be generated with a thin of 75 after a burn-in of 10,000 samples. The number of samples or thin may be increased as needed to reduce the MCSE/SD<0.01 as deemed necessary.
• Three chains will be used to calculate the gelman-rubin R statistic:
  ○ Chain 1: The starting value for all covariates in the model will be 0.
  ○ Chain 2: The starting value for all covariates in the model will be 2.
  ○ Chain 3: The starting value for all covariates in the model will be -2.
• The seeds used to for the three chains were generated using the ranuni function in SAS and are listed in Section 14.5.2.
• All post-burn-in samples will be used when creating outputs.

Model Checking & Diagnostics
• Posterior density plots and plots of the posterior samples (chains) will be produced for all the parameters in the model. • The posterior density for the adjusted mean change from baseline in E-RS: COPD score in each treatment group and differences versus placebo for each danirixin dose will be plotted. • The Gelman-Rubin R estimate from the three chains will be calculated for all parameters in the model and the differences from placebo for each danirixin dose. • Distributional assumptions underlying the model used for analyses using MMRM will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are

reasonable. Plots of residuals versus covariates and baseline versus response will also be examined.
Model Results Presentation
• The adjusted posterior mean change from baseline and the associated 90% equi-tailed CrI for each Month for each treatment. • The adjusted mean difference from placebo and the associated 90% equi-tailed CrI for each Month for each danirixin dose. • The probability that each treatment difference is less than 0, -0.5, -1, -1.5 and -2 for each month for each danirixin dose. • A figure of the posterior mean and 90% equi-tail CrI for each Month for each treatment.
Sensitivity and Supportive Analyses
• At the strategic interim a supportive analysis of monthly E-RS: COPD total score will be conducted to estimate the effect of actual treatment in the population of participants who were confirmed as having CMH according to SGRQ, were symptomatic at baseline, and did not experience a protocol deviation considered to impact efficacy. The population used will be the Symptomatic population; all other details will be the same as for the primary analysis. • At the strategic interim a further supportive analysis will be conducted to estimate the effect of the randomized treatment. The population used will be the ITT (according to randomized treatment). A 'treatment policy' strategy will be used to account for the intercurrent event of occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1). All E-RS: COPD data up the time of treatment discontinuation or Month 6 (see Section 14.6.3) will be used in the analysis, regardless of any protocol deviation. A 'hypothetical' strategy will be used to account for the intercurrent event of treatment discontinuation. Data after treatment discontinuation will be considered MAR.

7.1.3.5.2. Frequentist MMRM Methodology Specification

Endpoint / Variables
• Change from baseline in monthly E-RS: COPD total score
Model Specification
• The following covariates will be included in the model: baseline, country, smoking status at screening, treatment, Month, Month*baseline and Month*treatment interactions, where Month is nominal. Month will consist of six levels (Month 1-Month 6), and treatment will consist of six levels (placebo and 5 active doses) • Two models will be fitted; one with a response variable of E-RS: COPD Total Score, and one with a response variable of change from baseline in E-RS: COPD Total Score. • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. If this method does not run, the residual method will be used instead • The OM option will be used to derive the least square (LS) means using coefficients which are based on the participants used in the analysis. The OM option requires an OM dataset which has a row for every participant-visit combination that contains all of the covariates used in the model and a macro variable containing the mean baseline for the participants used in the

analysis.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analyses using MMRM will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. Plots of residuals versus covariates and baseline versus response will also be examined.
Model Results Presentation
• LS mean and LS mean changes from baseline with their corresponding standard errors (SEs) for each Month and each treatment • Estimated treatment differences from placebo and corresponding 90% confidence intervals (CIs) and p-values for each Month and each danirixin dose. • A figure of LS mean changes from baseline and 90% CIs for each treatment by Month will be generated. • A figure of LS mean and 90% CIs for each treatment by Month will be generated. • The type III tests of fixed effects from the model will be presented.
Summary Results Presentation
• A figure of daily mean E-RS: COPD total and subscale scores over time (Days -7 to 168) for the PP population. • A figure of daily mean E-RS: COPD total and subscale scores over time by completer status (Days -7 to 168) for the PP population. • A figure of daily mean change from baseline E-RS: COPD total and subscale scores over time for the PP population. • A figure of daily mean (± SE) change from baseline E-RS: COPD total and subscale scores over time for each dose and placebo in a separate panel. This figure will be produced for the PP and Symptomatic populations (Strategic interim only). • A figure of daily mean (± SE) E-RS: COPD total and subscale scores over time (Days -7 to 168) for each dose and placebo in a separate panel. This figure will be produced for the PP population. • Summary statistics for baseline E-RS: COPD total and subscale scores for each treatment and overall for participants with non-missing score for each Month, for the PP and Symptomatic (Strategic interim only) population. • Summary statistics for raw and change from baseline monthly mean E-RS: COPD total and subscale scores for each month for each treatment, for the PP and Symptomatic population (Strategic interim only). • Empirical distribution function plot of E-RS: COPD Total Scores at Baseline and at Month 6.

7.2. Secondary Efficacy Analyses

The estimand is the effect of actual treatment in the population of participants who did not experience a protocol deviation considered to impact efficacy.

A supportive analysis will be conducted to estimate the treatment policy effect of the randomized treatment on the annual rate of HCRU exacerbations in all randomized and dosed participants.

7.2.1. Annual Rate of HCRU Exacerbations and Annual Rate of EXACT Events

7.2.1.1. Endpoint

Annual rate of moderate/severe HCRU exacerbations as defined in Section 14.6.3.

Annual rate of EXACT events as defined in Section 14.6.3.

7.2.1.2. Summary Measure

Rate ratio (also expressed as percentage rate reduction) for each danirixin dose vs. placebo

7.2.1.3. Population of Interest

PP population

7.2.1.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent events of interest are occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1) and treatment discontinuation. An 'as treated' strategy will be used to account for these events to estimate the effect if participants had not deviated from the protocol and remained on treatment. Only HCRU exacerbations/EXACT events prior to the occurrence of a protocol deviation considered to impact efficacy will be used in the analysis.

7.2.1.5. Statistical Analyses / Methods

7.2.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Annual rate of On-treatment moderate/severe HCRU exacerbations • Annual rate of On-treatment EXACT events
Model Specification

• Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate with a log link function
• Terms in the model:
  ○ Response: number of on-treatment, moderate/severe HCRU exacerbations or EXACT events per participant.
  ○ Categorical: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), country
  ○ Continuous: post-bronchodilator % predicted FEV1 (Screening)
  ○ An offset to account for the length of time on treatment for each participant will be

included in the model as $\log_e$ (length of time) as defined in Section 14.6.3.
    - Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.
    - All the terms in the model will follow a normal distribution with a mean of 0 and a SD of 100, except for dispersion which follows a gamma distribution with shape and inverse scale of 0.001.
- Three chains will be used to calculate the gelman-rubin R statistic:
    - Chain 1: The starting value for all covariates in the model will be the maximum likelihood estimation (MLE), except dispersion which will be 0.1.
    - Chain 2: The starting value for all covariates in the model will be 130% of the MLE, except for dispersion which will be 0.2.
    - Chain 3: The starting value for all covariates in the model will be 70% of the MLE, except for dispersion which will be 0.4.
- The seeds used to for the three chains were generated using the ranuni function in SAS and are listed in Section 14.5.2.
- Burn-in 2000, thin 5, and 10,000 MCMC samples will be generated for 2000 retained samples

Model Checking & Diagnostics

- The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulated envelopes as proposed by Atkinson (Atkinson, 1985).
- The Gelman-Rubin R estimate will be calculated for all parameters in the model and the rate ratios vs. placebo for each danirixin dose.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).

Model Results Presentation

- Model estimated median exacerbation/event rate and associated 90% CrI for each treatment group
- Median rate ratio and associated 90% CrI, percent reduction in annual exacerbation/event rate and associated 90% CI for each danirixin dose vs. placebo
- The probability that the true exacerbation rate ratio is less than 1, 0.9 and 0.8 for each danirixin dose will be presented
- A figure of the rate ratios and associated 90% CrIs for each danirixin dose vs. placebo

Summary Results Presentation

For HCRU exacerbations:

- Number and percent of participants reporting an exacerbation (mild, moderate, severe and moderate/severe), number and percent of participants with each number of moderate/severe exacerbations (0, 1, ≥2), the total number of exacerbations per treatment and annual raw exacerbation rate (as defined in Section 14.6.3). This table will be repeated for HCRU exacerbations that were treated with Antibiotics and will include the number and percentage of participants who were receiving ICS treatment at the time of the exacerbation.
- For each moderate/severe exacerbation, the outcome, severity, duration, whether the exacerbation led to hospitalization, systemic/oral corticosteroids being taken, antibiotics being taken, or emergency room visit.

For EXACT events:

- Number and percent of participants reporting an EXACT-defined event, number and percent of

participants with each number of EXACT-defined events (0, 1, ≥2), the number of EXACT-defined events and annual raw event rate (as defined in Section 14.6.3) will be summarized for all events and for recovered, censored and persistent worsening events separately for each treatment group. The duration and severity (indicated by the maximum observed value and duration) will be reported for all events.
Sensitivity and Supportive Analyses
• At the strategic interim a supportive analysis of HCRU exacerbations will be conducted to estimate the effect of the randomized treatment. The population used will be the ITT (according to randomized treatment). A 'treatment policy' strategy will be used to account for the intercurrent event of occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1). All on-treatment exacerbations up the time of treatment discontinuation will be used in the analysis, regardless of any protocol deviation. An 'as treated' strategy will be used to account for the intercurrent event of treatment discontinuation – no exacerbations will be recorded after treatment discontinuation/study withdrawal.

7.2.2. Time to First HCRU Exacerbation and EXACT Event

7.2.2.1. Endpoint

Time to first moderate/severe HCRU exacerbation as defined in Section 14.6.3.

Time to first severe HCRU exacerbation as defined in Section 14.6.3.

Time to first EXACT event as defined in Section 14.6.3.

7.2.2.2. Summary Measure

Hazard ratio (also expressed as percentage risk reduction) for each danirixin dose vs. placebo)

7.2.2.3. Population of Interest

PP population

7.2.2.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent events of interest are occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1) and treatment discontinuation. An 'as treated' strategy will be used to account for these events to estimate the effect if participants had not deviated from the protocol and remained on treatment. Only first exacerbations/EXACT events prior to the occurrence of a protocol deviation considered to impact efficacy will be used in the analysis.

7.2.2.5. Statistical Analyses / Methods

7.2.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Time to first On-treatment moderate/severe HCRU exacerbation • Time to first On-treatment severe HCRU exacerbation • Time to first On-treatment EXACT event
Model Specification

• Bayesian proportional hazards model
• Terms in the model:
  ○ Response: time to first on-treatment, moderate/severe HCRU exacerbation or EXACT event
  ○ Categorical: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), country
  ○ Continuous: post-bronchodilator % predicted FEV1 (Screening)
  ○ Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.
  ○ All the terms in the model will follow a normal distribution with a mean of 0 and a SD of 100
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
• Three chains will be used to calculate the gelman-rubin R statistic:
  ○ Chain 1: The starting value for all covariates in the model will be the MLE, except dispersion which will be 0.1.
  ○ Chain 2: The starting value for all covariates in the model will be 130% of the MLE, except for dispersion which will be 0.2.
  ○ Chain 3: The starting value for all covariates in the model will be 70% of the MLE, except for dispersion which will be 0.4.
• The seeds used to for the three chains were generated using the ranuni function in SAS and are listed in Section 14.5.2.
• Burn-in 2000, thin 5, and 10,000 MCMC samples will be generated for 2000 retained samples
• Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Model Results Presentation
• Hazard ratio and the percent reduction in risk for each danirixin dose compared with placebo with associated 90% CrI. • The probability of having an event, 90% CrI and first quartile and median time to event for each treatment group will be presented. • The probability that the true hazard ratio is less than 1 for each danirixin dose will be presented.

• Kaplan-Meier curves showing the probability of having an event over time for each treatment group separately plotted on the same figure

7.2.3. E-RS: COPD Total and Subscale Scores Responder Analysis

7.2.3.1. Endpoint

Response according to E-RS: COPD total score, subscale scores, SGRQ total score or CAT score as defined in Section 14.6.3.

7.2.3.2. Summary Measure

Ratio of odds of being a responder vs. not for each danirixin dose vs. placebo

7.2.3.3. Population of Interest

PP population

7.2.3.4. Strategy for Intercurrent (Post-Randomization) Events

A 'hypothetical' strategy will be used to account for the intercurrent events of occurrence of a protocol deviation considered to impact efficacy during the treatment period (see Appendix 1) and treatment discontinuation, to estimate the effect if participants had not deviated from the protocol and remained on treatment. Only response data prior to the occurrence of a protocol deviation considered to impact efficacy or treatment discontinuation will be used in the analysis. Subsequent data up to Month 6 will be assumed to be missing at random (MAR).

7.2.3.5. Statistical Analyses / Methods

7.2.3.5.1. Statistical Methodology Specification

Endpoint / Variables
• Response according to E-RS: COPD total score, subscale scores, SGRQ total score or CAT score
Model Specification

• Generalized linear mixed model
• Terms in the model:
  ○ Dependent : response (yes/no)
  ○ Categorical : treatment group, smoking status (screening), country, visit/month
  ○ Continuous : baseline
  ○ Interaction : baseline*visit/month, treatment group*visit/month
• The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits/months where the assessment in question is scheduled to be performed.
• Computation of confidence intervals for the odds ratios is based on the individual Wald tests.

Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Model Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit/month • Odds ratio for comparison of each danrixin dose with placebo, with associated 90% CI and p-value

7.2.4. SGRQ Total Score and CAT Score

SGRQ total score and CAT score at each visit will be analysed using the same methodology as for E-RS: COPD total and subscale scores longitudinal analysis (as described in Section 7.1.3.5.1). Visit will be substituted for Month. A figure of mean and 90% CIs for each treatment over time will be generated for SGRQ Total Score and CAT Score.

7.2.5. Rescue Use

The monthly mean number of puffs of rescue use per day according to diary card data and the monthly mean number of occasions of rescue use per day according to sensor data and the monthly percentage of rescue-free days according to diary card data and according to sensor data will be analysed using the same methodology as for E-RS: COPD total and subscale scores longitudinal analysis (as described in Section 7.1.3.5.2). A figure of daily mean number of puffs of rescue medication per day using diary data over time and daily mean number of occasions of rescue medication per day using sensor data over time will be generated for the PP population.

Additional analysis of rescue use according to sensor data may be performed and will be defined in a separate RAP.

7.2.6. Physical Activity

Assessment of physical activity during clinical visits (C-PPAC) has been developed to capture experience of physical activity in participants with COPD. This physical activity data will be combined with activity monitor data to assess physical activity experience according to the IMI PROactive User Guide (14JUN16). A PROactive Total Score and two domain scores (amount and difficulty) will be derived.

Raw and change from baseline PROactive Total Score and Domain scores (Amount and Difficulty) will be summarized.

For the strategic interim, the responses to the C-PPAC questions at each visit will be summarized.

Additional analysis of activity monitor data may be performed and will be defined in a separate RAP.

7.3. Exploratory Efficacy Analyses

7.3.1. E-RS: COPD Total Score

For the final analysis the list of subgroups may be amended.

Exploratory Statistical Analyses
Model Specification
For the PP population, an assessment of whether the effect of treatment on E-RS: COPD Total Score is modified by: o Baseline E-RS: COPD Total Score (continuous) (Strategic Interim only) o Smoking Status at Screening o Country (Strategic Interim only) will be made by fitting separate repeated measures models, identical to the MMRM model described in Section 7.1.3.5.2 but also including additional terms for the treatment by factor interaction. An assessment will be made of whether the effect of treatment on E-RS: COPD Total Score is modified by the following factors (as defined in Section 5.4.2): o Percent Predicted FEV1 at Screening (continuous) o Baseline CAT Score (continuous) o Exacerbation history (Strategic Interim only) o COPD Medication at Baseline (Strategic Interim only) o CMH status at baseline (Strategic Interim only) o Season (Strategic Interim only) This will be made by fitting separate repeated measures models, identical to the model described above but also including additional terms for the factor and the treatment by factor interaction. If an interaction from these analyses is significant at the 10% level it implies that the effect of treatment on E-RS: COPD Total Score is modified by the factor. The analysis will be run by each level of the factors as listed below regardless of significance level (excluding any groups with sparse data): o Baseline E-RS: COPD Total Score <10, ≥10 (Strategic Interim only) o Smoking Status at Screening - Former, Current o Country (Strategic Interim only) o Percent Predicted FEV1 at Screening <50, ≥50 o Baseline CAT Score <10, ≥10 o Exacerbation history (history of ≥2 moderate/severe exacerbations, <2 moderate/severe exacerbation) (Strategic Interim only) o COPD Medication at Baseline (ICS+LABA+LAMA vs. ICS+LABA vs. LABA+LAMA vs. Other COPD medication) (Strategic Interim only) o CMH +, - (Strategic Interim only) o Season (The estimates from this model will be presented for each season.) (Strategic Interim only)
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analyses using MMRM will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. Plots of residuals versus covariates and baseline versus response will also be examined.

Exploratory Statistical Analyses
Model Results Presentation
• The interaction p-values from the interactions of treatment with the factors above will be presented. • Comparisons of each danirixin dose with placebo for each level of each categorical subgroup. • LS Mean changes from baseline estimates for each treatment by visit (except for season) along with 90% CIs will be obtained for each level of the subgroup. • LS Mean changes from baseline estimates for each treatment along with 90% CIs will be obtained for each level of the season subgroup. • LS Mean changes from baseline estimates and 90% CIs will be plotted against treatment in separate panels for each level of the factor for Month 6 (except for season).LS Mean changes from baseline estimates and 90% CIs will be plotted by treatment for each level of the season subgroup. • If an interaction between treatment and factor is significant at the 10% level an additional plot of LS Mean changes from baseline and 90% CIs against treatment by Month will be produced with a separate plot for each level of the factor (except for season).

7.3.2. CAT Score

CAT score will be analysed using the same methodology as for E-RS: COPD total scores exploratory statistical analysis (as described in Section 7.3.1).

7.3.3. Time to First Clinically Important Deterioration

Following the Strategic Interim, the study team decided not to report this exploratory endpoint.

7.3.4. SGRQ Domain Scores

Raw and change from baseline SGRQ domain scores will be summarized.

7.3.5. Participant Global Assessments

Participant global assessments of severity, change in severity, activity limitation and change in activity limitation will be summarized.

8. SAFETY ANALYSES

Details of the planned displays including the population to be used for each display and which displays are produced for the strategic interim are presented in Appendix 11. Additional details are provided below.

The estimand is the effect of actual treatment in the population of participants who were randomized and dosed. All collected data will be included in reporting as described below. Non-recorded missing data following study withdrawal will not be imputed.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards.

8.2. Adverse Events of Special Interest Analyses

AESI have been defined as AEs which have specified areas of interest for the COPD population. A list of Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) and other groupings for AESI is provided in Section 14.6.4

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory testsand liver function tests will be based on GSK Core Data Standards.

8.4. Spirometry

The estimand is the effect of actual treatment in the population of participants who were randomised and dosed.

A frequentist MMRM analysis will be performed on spirometry data.

8.4.1. Endpoint

Change from baseline in post-BD FEV1

Change from baseline in post-BD FVC

8.4.2. Summary Measure

The summary measure is the adjusted mean difference from placebo for each danirixin dose.

8.4.3. Population of Interest

mITT population.

8.4.4. Strategy for Intercurrent (Post-Randomization) Events

The intercurrent event of interest is treatment discontinuation. A 'hypothetical' strategy will be used to account for this event. All recorded data up to the time of treatment discontinuation will be included in the analysis. Subsequent data up to Day 168 will be assumed to be missing at random (MAR).

8.4.5. Statistical Analyses / Methods

8.4.5.1. Frequentist MMRM Methodology Specification

Endpoint / Variables
• Change from baseline in post-BD FEV1 • Change from baseline in post-BD FVC
Model Specification
• The following covariates will be included in the model: baseline, country, smoking status at screening, treatment, Visit, Visit *baseline and Visit *treatment interactions, where Visit is nominal. Visit will consist of two levels (Day 84 and 168), and treatment will consist of six levels (placebo and 5 active doses) • Two models will be fitted; one with a response variable (FEV1 or FVC), and one with a response variable of change from baseline (FEV1 or FVC). • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. If this method does not run, the residual method will be used instead • The OM option will be used to derive the least square (LS) means using coefficients which are based on the participants used in the analysis. The OM option requires an OM dataset which has a row for every participant-visit combination that contains all of the covariates used in the model and a macro variable containing the mean baseline for the participants used in the analysis.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analyses using MMRM will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. Plots of residuals versus covariates and baseline versus response will also be examined.
Model Results Presentation
• LS mean and LS mean changes from baseline with their corresponding standard errors (SEs) for each visit and each treatment • Estimated treatment differences from placebo and corresponding 90% confidence intervals (CIs) and p-values for each visit and each danirixin dose. • A figure of LS mean changes from baseline and 90% CIs for each treatment by visit will be generated. • The type III tests of fixed effects from the model will be presented.

Summary Results Presentation
• Summary statistics for baseline post-BD FEV1, FVC and FEV1/FVC for each treatment and overall for participants with non-missing assessments for each Visit, for the mITT population. • Summary statistics for raw and change from baseline post-BD FEV1, FVC and FEV1/FVC for each visit for each treatment, for the mITT population. • A figure of mean and 90% CIs for each treatment by visit (including baseline, Day 84 and Day 168) will be generated for post-BD FEV1, FVC and FEV1/FVC.

8.5. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Derived Pharmacokinetic Parameters

PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from the blood concentration-time (dry blood spot) data at Visit 3 and 10, as data permits for participants in the PK sub-set collecting PK samples at pre-dose, 0.5. 1. 2. 4. 6, 8, 10, 12 hours post-dose.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Tlast	Time of last quantifiable concentration

NOTES:

- Additional parameters may be included as required.

9.1.2. Statistical Analyses / Methods

No formal statistical analysis of the dry blood spot PK concentrations or PK parameters will be performed. Details of the planned displays are provided in Appendix 11 and will be based on GSK Data Standards and statistical principles.

9.2. Exploratory Pharmacokinetic Analyses

9.2.1. Derived Pharmacokinetic Parameters

Note: Approximately 20% of the wet whole blood samples collected at Visit 3 will be analysed for danirixin concentrations to provide an analytical comparison between dried blood spot and wet whole blood sample results. The expectation is that samples selected will mainly come from those samples provided by participants in the PK sub-set (i.e. collecting samples over 12 hours) and be distributed across danirixin treatment groups.

PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from the blood concentration-time (wet whole blood) data at Visit 3, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
Tlast	Time of last quantifiable concentration

NOTES:

- Additional parameters may be included as required.

9.2.2. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11 and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

9.2.2.1. Statistical Methodology Specification

An extension of the Bland and Altman approach [Bland, 1986; Bland, 1999] will be used to quantify the agreement between the assay methods using log-transformed data, including hematocrit in the model. Age and weight will also be added one at a time in a model building approach and their significance in the model will be assessed. Limits of agreement and the coefficient of variation will be assessed to determine the agreement of the assay methods and whether wet whole blood assay is comparable to dry blood spot assay.

A sensitivity analysis will be performed excluding dry blood spot concentrations above the assay higher level of quantification of 1000 ng/mL.

Endpoint / Variables
• Log-transformed Danirixin blood concentration and pharmacokinetic parameter (Cmax and AUC(0-t)) data
Model Specification
• The Bland and Altman method will be used. • The following covariates will be included in the model: haematocrit, age and weight.
Model Results Presentation
• Separate outputs will be produced for Danirixin concentration and pharmacokinetic parameters (although both will be analyzed using the same model) • Estimates of intercept and slope on log-scale for Danirixin concentration and pharmacokinetic parameters, bias at concentration is 0, %CVw, geometric means and limit of agreement at concentration is 0. • Comparative plots of individual blood concentration and pharmacokinetic parameter data. • Supportive SAS output from statistical analysis.
Sensitivity and Supportive Analyses
• A sensitivity analysis excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL will be performed.

10. POPULATION PHARMACOKINETIC ANALYSES

PK data from this study may be combined with historic data for the purposes of population PK (PopPK) modelling which would be the subject of a separate analysis plan and would be presented separately from the main CSR.

To support this analysis a PopPK dataset will be generated. The details for the dataset specifications are provided in Appendix 9.

11. BIOMARKER ANALYSES

C-reactive protein and fibrinogen data will be summarized in the same way as laboratory data. Summary tables and boxplots for each treatment by visit (including screening, baseline, Day 84 and Day 168) will be generated for the mITT populations and also for the subset of subjects who have an event in the 'Infective pneumonia' SMQ.

Exploratory biomarker analysis will be the subject of a separate RAP.

12. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Graphical assessment of the relationship between individual danirixin exposure and PD endpoints will be conducted.

Contingent on any PK/PD relationship(s) being identified from the graphical assessment a PK/PD dataset will be generated. The details for the methodology and dataset specifications will be provided in a separate document after review of the graphical assessment of the relationship between PK and PD endpoints.

12.1. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11 and will be based on GSK Data Standards and statistical principles.

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14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

14.1.1. Exclusions from Per Protocol Population

A participant meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Inclusion #2 – FEV1/FVC ratio >=0.70 or % predicted FEV1<40% at Screening
02	Inclusion #4 – <2 historical exacerbations or one historical exacerbation with screening fibrinogen <3 g/L
03	Inclusion #5 - Smoking history of <10 pack years at Screening
04	Exclusion #4 - Screening visit is less than 14 days since the completion of a course of antibiotics or oral steroids for a COPD exacerbation
05	Exclusion #14 - Use of PDE4 inhibitors within 30 days of Screening
06	Exclusion #26 - Oxygen use that is not PRN at Screening

At the strategic interim a participant meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
07	Xanthines at any time between the day after screening and end of treatment
08	PDE4 inhibitors at any time between screening and end of treatment
09	Chronic use (more than 3 months) of erythromycin or azithromycin for between screening and end of treatment
10	Participants who stopped study medication for more than 14 days
11	Blind broken

For the final analysis a participant meeting any of the following criteria will have data excluded from the time of the deviation. If a prohibited medication is taken prior to randomisation the participant will be excluded from the Per Protocol population.

Number	Exclusion Description
07	Xanthines at any time between the day after screening and end of treatment
08	PDE4 inhibitors at any time between screening and end of treatment
09	Chronic use (more than 3 months) of erythromycin or azithromycin between screening and end of treatment
10	Participants who stopped study medication for more than 14 days will be excluded from the PP analyses from the time they stopped taking study medication.
11	Data excluded from date of breaking of blind.

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			-7	1	14	28	56	84	112	140	168		
Assessment Window	-30 d		± 0d	+ 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d		
Eligibility													
Informed consent	X												
Genetic Sample Informed Consent[b]	X												
Demography	X												
COPD Exacerbation History	X												
Pre-Screening Fibrinogenc	X												
Smoking History[d]		X											
Smoking Status[d]		X	X										
Inclusion and Exclusion criteria		X											
Medical history[e]		X											
Full physical examination including height and weight		X											

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**± 0d**	**+ 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**		
Chest x-ray (CXR)[f]		X											
HIV, Hepatitis B and C screening[g]		X											
Pulse Oximetry		X											
Additional Eligibility and In Study Assessments													
Verify Eligibility[h]			X	X									
Brief Physical				X				X			X	X	X
Urine or serum pregnancy test[i]		X		X		X	X	X	X	X	X	X	
Laboratory assessments (clinical chemistry (includes liver chemistries), hematology, urinalysis)		X		X		X					X	X	X
Additional Liver chemistries only					X		X	X					
12-lead ECG		X		X		X		X			X	X	
Vital signs	X	X		X		X		X			X	X	
Spirometry		X		X				X			X	X	
Randomization				X									

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**± 0d**	**+ 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**		
Dispense Study Medication				X		X	X	X	X	X			
Dispense log pad and provide training			X										
Dispense MDI sensors and provide training			X										
Dispense physical activity monitor and provide training			X										
Study treatment				←==========→									
Study treatment compliance (ediary)				←==========→									
Collect IP						←==========→						X	X
Collect MDI sensors												X	X
Collect physical activity monitor												X	X
Collect log pad												X	X
Adverse Event (AE) review				←==========→								X	X
Serious Adverse Event (SAE) review	←==========→											X	X

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**± 0d**	**+ 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Outcomes Assessments													
COPD Exacerbations			←==========→									X	X
EXACT-PRO[j]			←==========→										
Rescue Medication Use[k]			←==========→										
SGRQ-C				X				X			X	X	
COPD Assessment Test				X				X			X	X	
PROactive Questionnaire[l]				X				X			X		
Physical Activity Monitor[l]			X					X			X		
Participant Global Impression of COPD Severity			X										
Participant Impression of Change in COPD Severity					X	X	X	X	X	X	X	X	

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		**± 0d**	**+ 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**		
Participant Global Impression of Activity Limitation			X										
Participant Impression of Change in Activity Limitation					X	X	X	X	X	X	X	X	
Genetic, Pharmacokinetic and Biomarker Blood Collections													
Blood sample for Genetics				X									
Blood sample for pharmacokinetics (PK)[m]				X			X	X			X		
Blood sample for Fibrinogen				X				X			X	X	
Blood sample for CRP				X				X			X	X	
Blood Sample for Exploratory Biomarkers				X				X			X	X	

Procedure	Pre-Screening[a] (Visit 0)	Screening[a] (Visit 1)	Study Visits									Early Withdrawal	Follow Up (up to 28 days post last dose)
			2	3	4	5	6	7	8	9	10		
Study Day			**-7**	**1**	**14**	**28**	**56**	**84**	**112**	**140**	**168**		
Assessment Window	**-30 d**		± **0d**	+ **3d**	± **3d**	± **3d**	± **3d**	± **3d**	± **3d**	± **3d**	± **3d**		

a. Pre-screening and screening visits may be completed on the same day.
b. Agreeing to the genetic sample consent is not required for study participation.
c. A pre-screening plasma fibrinogen measurement is only required for participants with 1 COPD exacerbation in the prior year.
d. Smoking status /history assessed at screening: smoking status rechecked at Visit 2
e. Includes substance usage, past and present medical conditions and family history of premature CV disease.
f. See inclusion/exclusion criteria for CXR screening requirement
g. Hepatitis B (HBsAg) and Hepatitis C (HepC antibody) testing is required. If testing otherwise performed within 3 months prior to the first dose of study treatment, testing at screening is not required. Hepatitis C RNA testing is optional; however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease.
h. Participant's clinical status should be reviewed.
i. Pregnancy testing only required for women of child bearing potential (WOCBP). A positive urine pregnancy test requires confirmation with a serum pregnancy test.
j. E-RS: COPD is a subset of EXACT-PRO and is not a separate assessment.
k. Rescue medication use will be assessed via e-diary and MDI sensor.
l. The Clinic Visit PROactive Physical Activity in COPD tool will be assessed in a subset of approximately 50% of study participants
m. Pre-dose PK samples will be collected in all participants at Visits 3, 6, 7, and 10. In a subset of participants (approx. 50 participants at each dose level) at Visit 3, PK samples will be collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. In a subset of participants (approx.. 50 participants at each dose level) at Visit 10, PK samples will be collected at pre-dose, 0.5. 1. 2. 4. 6, 8, 10, 12 hours post-dose.

14.3. Appendix 3: Assessment Windows

In general, data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol. For example, if a participant recorded values for the Day 28 visit that were actually made on the 21st day of treatment, they will be presented as Day 28 values in the summary tables.

Participants that withdraw from the study at the time of a scheduled study visit will have data collected in the eCRF as part of the scheduled study visit. In order to collect all questionnaires that are scheduled to be performed at the Early Withdrawal (EW) Visit, eDiary data is reported as an EW Visit. If the date of the EW diary assessment is the same as the date of a scheduled visit date from the eCRF and there is no diary data present at the scheduled visit in question, the EW diary data will be listed, summarized and analysed as part of the scheduled visit (if the diary data was scheduled to be performed at the visit in question).

14.4. Appendix 4: Study Phases

14.4.1. Study Phases

Assessments and events collected outside scheduled study visits will be classified into study phases according to the time of occurrence relative to the start and/or stop date of study treatment. The 'worst case-post baseline' derivation for summaries will consider all scheduled and unscheduled measurements that have been assigned a treatment phase of 'On-treatment'.

14.4.1.1. Study Phases for Diary Data

Diary data (including EXACT events) treatment states are specified in Section 14.6.3.

14.4.1.2. Study Phases for Concomitant Medication

COPD medication combinations taken at screening will include all COPD medications that were taken on the day of the screening visit, excluding medications that stopped on the day of the screening visit.

Treatment phases for summaries of COPD and non-COPD concomitant medications will be assigned as follows:

Study Phase	Definition
Prior	Medications taken on or before the day before treatment start date defined as: (conmed start date < treatment start date or 'Taken prior to study?' is 'Yes' or study treatment not started or conmed start date is missing) Note: prior concomitant medication data will only be summarized for COPD medications. All screening data will be listed.
On-treatment	If study treatment stop date > study treatment start date then this includes medications taken between the study treatment start date and study treatment stop date - 1 (inclusive) defined as follows: (conmed start date < study treatment stop date or conmed start date is missing) and (conmed stop date >= study treatment start date or (conmed stop date is completely missing and study treatment start date is non-missing)) If study treatment stop date = study treatment start date then this includes medications taken on the study treatment start date (which is equal to the study treatment stop date) defined as follows. (conmed start date <= study treatment stop date or conmed start date is missing) and (conmed stop date >= study treatment start date or (conmed stop date is completely missing and study treatment start date is non-missing))
Post-treatment	If study treatment stop date > study treatment start date then this includes medications taken after the study treatment stop date defined as follows: (conmed stop date >= study treatment stop date or (conmed stop date is completely missing and study treatment stop date is non-missing)) If study treatment stop date = study treatment start date then this includes medications taken after the study treatment stop date + 1 defined as follows. (conmed stop date > study treatment stop date or (conmed stop date is completely missing and study treatment stop date is non-missing))

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken.
- See Section 14.7.2.1 for handling of partial dates.
- If the study treatment stop date is missing, it will be imputed as described in Section 14.6.1.

14.4.1.3. Study Phases for Event Data

Classification of a HCRU exacerbation/AE as having onset on-treatment will be made with reference to the study treatment start and stop dates and the event onset date. If the event onset date is missing, then the event will be considered on-treatment.

Study Phase	Definition
Pre-treatment	If onset date is prior to treatment start date Start Date < Study Treatment Start Date
On-treatment	If onset date is on or after treatment start date & on or before treatment stop date + 3. Study Treatment Start Date ≤ Start Date ≤ Study Treatment Stop Date + 3 days
Post-treatment	If onset date is after treatment stop date + 3. Start Date > Study Treatment Stop Date + 3 days

Note: assume on-treatment unless there is evidence to the contrary

14.4.1.4. Study Phases for Other Data

All data collected at scheduled study visits after Day 1 will be considered on-treatment. Any data collected at unscheduled visits (ie, laboratory data, vital signs, ECGs, spirometry, CAT and SGRQ) will be classified as on-treatment based on the study treatment start date (and time, if available) and study treatment stop date and the date (and time, if available) of the visit/assessment. If the visit/assessment date is missing, then the event will be considered on-treatment.

Study Phase	Definition
Pre-treatment	If assessment/visit date (and time) is on or prior to treatment start date (and time) Assessment/Visit Date (and time) ≤ Study Treatment Start Date (and time)
On-treatment	If assessment/visit date (and time) is after treatment start date (and time) & on or before treatment stop date + 3. Study Treatment Start Date (and time) < Assessment/Visit Date (and time) ≤ Study Treatment Stop Date + 3 days
Post-treatment	If assessment/visit date is after treatment stop date + 3. Assessment/Visit Date > Study Treatment Stop Date + 3 days

Note: assume on-treatment unless there is evidence to the contrary

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: GSK1325756
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards for the strategic interim and CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1].	
Generation of RTF Files	
• RTF files will be generated for strategic interim and final reporting efforts	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.24: General Principles
  • 5.01 to 5.08: Principles Relating to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats

• GSK IDSL Statistical Principle 4.24 for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
• Numeric data will be reported at the precision collected on the eCRF.
• The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
  o E-RS: COPD and SGRQ will have a min and max to 1 decimal places (dp) and then follow IDSL standards for reporting other summary statistics.
  o CAT will have a min and max to 0 dp and then follow IDSL standards for reporting other summary statistics.
• Categories will be based on rounded values to the precision collected on the eCRF, i.e., categories of % predicted FEV1 will be based on the rounded (to 1 dp) values of the variable FEV1PDPC
• Summaries of continuous data will include number of participants, mean, SD, median, minimum and maximum and for C-RP and fibrinogen outputs the 25th and 75th percentile.
• Percentages between 1% and 99%, inclusive, will be rounded to integers. Percentages greater than 0%, but less than 1%, will be reported as <1%, and percentages greater than 99%, but less than 100%, will be reported as >99%.

Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.

- Actual time will be used for calculation of times to events and Kaplan-Meier plots.

- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits

- Unscheduled visits will not be included in summary tables and/or figures except as part of a maximum/minimum/worst case post-baseline assessment or if they are assigned as the baseline assessment as detailed in Section 5.2.
- All unscheduled visits will be included in listings.

Cardiovascular Event Reports

- Laboratory results, ECG results/findings and vital signs measurements collected as part of cardiovascular event reports will not be included in any tables, listings or any minimum/maximum post-baseline assessments.

Time to Event Results

- For all time to event analyses, the first quartile and median time to event will be presented. If less than 25% of participants experienced the event within a treatment group then the first quartile will be displayed as NA (not applicable) for that treatment. If less than 50% of participants experienced the event within a treatment group then the median will be displayed as NA for that treatment.

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to IDSL Statistical Principals 7.01 to 7.13.

Seeds for Bayesian Analyses

- The seeds used to for the Bayesian analyses were generated using the ranuni function in SAS. The same seeds should be applied for all endpoints and populations.

Chain	Seed
1	2619
2	413
3	9243

14.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487 and PKOne documents. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. Additionally, include geometric mean and 90% CI for the summary of blood concentration data.
NONMEM/Pop PK File	PopPK file (CSV format) for the PopPK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Appendix 9.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	None
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Potential Clinical Importance criteria at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Worst case post-baseline" row of related summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

Study Treatment Stop Date

• If the study treatment stop date is missing, it will be imputed as follows:
  • If any of EW Visit date, Visit 10 (Day 168) date or date of death are non-missing then the study treatment stop date will be imputed as the minimum of (EW Visit date, Visit 10 (Day 168) date, date of death, date that all study treatment containers were returned).
  • For all other missing treatment stop dates, the last recorded exposure start or stop date will be used.
• For ongoing participants at the strategic interim, treatment stop date will be imputed as 5SEP2018

Study Completion Definition
• A participant is considered to have completed the study if they have not withdrawn and attended Visit 10.

14.6.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any participant with a missing day will have this imputed as day '15'.
  ○ Any participant with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.
• Age will be calculated based on the Pre-screening visit date.
• Age group categories are 18-64, 65-74, 75-84, >=85

Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]

Baseline Characteristics

% Predicted Normal FEV1 at Screening

- The following categories will be derived: <50%, >=50%

Smoking Status

- If the last smoked date (SUSMLSDT) is missing and a partial date (SUSMLSD) is not missing, then the following imputation should be applied to the partial smoking date for use in the reclassification of smoking status calculation:
  - '01' will be used for the day and 'Jan' will be used for the month.
- Former smokers will be reclassified as current smokers if screening date – last smoked date < 183 days.

Chronic Mucus Hypersecretion

- A participant is considered to have CMH (CMH+) if baseline SGRQ Q1(cough) = Most or several days a week AND baseline SGRQ Q2 (phlegm) = Most or several days a week.
- A participant is considered not to have CMH (CMH-) if baseline SGRQ Q1(cough) not equal to Most or several days a week OR baseline SGRQ Q2(phlegm) not equal to Most or several days a week and both questions are non-missing at baseline.
- Otherwise participants are considered to have a missing CMH status.

Baseline E-RS: COPD Total Score Categories

- The following categories will be derived for baseline E-RS: COPD Total Score
  - <8, >=8
  - <10, >=10
  - <12, >=12

Exacerbation History Categories

- Exacerbations (historical) will be classified as follows:
  - Mild: Managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)
  - Moderate: Requiring oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation)
  - Severe: Requiring hospitalisation
  - Moderate/severe: Requiring oral/systemic corticosteroids and/or antibiotics or hospitalisation.
- The total number of moderate/severe exacerbations will be categorized as ≤1, ≥2 for inclusion as a covariate in statistical models.

GOLD Grade 1-4 at Screening

- Participants will be classified into Global Initiative on Obstructive Lung Disease (GOLD) Grades 1-4 using the post-bronchodilator percent predicted FEV1 assessment at Screening:
  - GOLD Grade 1 (Mild): percent predicted FEV1 ≥80%
  - GOLD Grade 2 (Moderate): 50%≤ percent predicted FEV1 <80%
  - GOLD Grade 3 (Severe): 30%≤ percent predicted FEV1 <50%
  - GOLD Grade 4 (Very Severe): percent predicted FEV1 <30%

GOLD Grade A-D at Screening

- Participants will be classified into GOLD Grades A-D definitions as follows:

  A. Low risk, less symptoms: baseline CAT < 10 AND GOLD Grade 1-2 AND ≤1 exacerbation; (no hospitalizations for exacerbations), prior year.

  B. Low risk, more symptoms: baseline CAT >= 10 AND GOLD Grade 1-2 AND ≤1 exacerbation (no hospitalizations for exacerbations), prior year

  C. High risk, less symptoms: baseline CAT < 10 AND either GOLD Grade 3-4 OR ≥ 2 exacerbations, prior year OR >=1 exacerbation leading to hospitalization, prior year

  D. High risk, more symptoms: baseline CAT >= 10 AND either GOLD Grade 3-4 OR ≥ 2 exacerbations, prior year OR >=1 exacerbation leading to hospitalization, prior year

Baseline Characteristics

Participant Disposition

- For Kaplan-Meier plots of study withdrawal over time, censoring will be performed as follows:
  - Participants are represented from their Day 1 date to the date of early withdrawal from the study (or date of death). Participants that completed the study are censored at the earliest of the date of completion and Day 168.

Medical Conditions and Concomitant Medications

Respiratory Medication Class

- COPD concomitant medications will be grouped into the following RMCs based on pre-defined code lists derived from ATC classifications:
  - Androgens and Estrogens
  - Anti-IgE, Anti-IL5
  - Anticholinergic
  - Antiinfectives (antibiotics, antiseptics only)
  - Antimycotics
  - Antivirals
  - Beta 2 Agonist
  - Corticosteroid – Inhaled
  - Corticosteroid – Depot
  - Corticosteroid – Systemic, oral, parenteral and intra-articular
  - Corticosteroid – Other
  - Leukotriene Receptor Antagonist
  - Long-acting anticholinergic
  - Long-acting beta-2 agonist
  - Mucolytics
  - Nedocromil or Cromolyn Sodium
  - Oxygen
  - PDE4 Inhibitors
  - Short-acting anticholinergic
  - Short-acting beta-2 agonist
  - Xanthine
  - Other medication given for exacerbation
  - Other COPD medication

COPD Medication Combination

- COPD medications will be summarized at the following time points:
  - At Screening: Taken on the day of the Screening visit excluding medications that stopped on the day of the Screening visit
  - At Baseline: Taken on the day of start of treatment
  - At Month 6: Taken during Month 6 (Study Day 141 to earliest of (Study day 168 and day before study treatment stop date))
- Medication combinations of all RMC categories will be derived. Medications will be summarized based on individual and combinations of the following RMC categories, with or without other medications:
  - ICS
  - LABA
  - LAMA
  - Xanthine
  - PDE4 inhibitor
  - Anti-IgE, Anti-IL5

Medical Conditions and Concomitant Medications

Cardiovascular Risk Factors

- Subjects with at least one of the following current or past medical conditions at Screening will be classed as having cardiovascular (CV) risk factor at screening. The number of CV risk factors at Screening (0, 1, or >=2) will be derived.
  - Coronary artery disease
  - Myocardial infarction
  - Arrithymia
  - Congestive heart failure
  - Hypertension
  - Cerebrovascular accident
  - Hypercholesterolemia
  - Diabetes mellitus

Compliance

Treatment Compliance

Compliance= (tablets issued–tablets returned) x 100 / 2 x (treatment stop date – treatment start date +1)

If any count of tablets returned is missing overall compliance will be set to missing.

- Compliance will be categorized as follows:
  < 80 %
  ≥ 80 % to < 95 %
  ≥ 95 % to ≤105 %
  >105 % to ≤120 %
  >120 %
- If a participant received a treatment other than the randomized treatment during the study, the compliance will still be calculated using data from all containers received and overall treatment start and stop dates.

Daily Diary Compliance

Overall compliance= (number of days with non-missing data between study treatment start and the earliest of (Study day 168 and day before study treatment stop)) x 100 / (Earliest of (Study day 168 and day before study treatment stop date) – treatment start date +1)

- Overall compliance will be categorized as follows:
  < 50 %
  ≥ 50 % to < 60 %
  ≥ 60 % to < 70 %
  ≥ 70 % to < 80 %
  ≥ 80 % to < 90 %
  ≥ 90 % to ≤100 %

Baseline and Monthly compliance= number of days with non-missing data between periods defined in Section 14.6.3

- Baseline compliance will be categorized as follows: Number of days completed <4, ≥4
- Monthly compliance will be categorized as follows: Number of days completed <10, 10-20, >20

Exposure

Exposure to Study Treatment

Duration of exposure to study treatment is calculated as (treatment stop date – treatment start date +1).

The following exposure categories will be derived:

≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks and ≥24 weeks. An additional category of 23-25 weeks will also be summarized.

14.6.3. Efficacy

Daily eDiary endpoints

General

Participants were instructed to complete the daily eDiary in the evening (typically at bedtime). The parameters collected include rescue use and EXACT-PRO scores.

The tables below show which daily eDiary records are used to calculate the daily eDiary parameters for each period. Any diary data collected after the minimum of (Day 168 and the day before study treatment stop date) will not be slotted.

To be used for rescue use endpoints and E-RS: COPD total and subscale scores:

Period	First day	Last day
Baseline[1]	Latest of (7 days before Study treatment start date (Day 1) and day of Visit 1 (Screening))	Day before Day 1 of study treatment
Month 1[1]	Study day 1	Study day 28
Month 2[1]	Study day 29	Study day 56
Month 3[1]	Study day 57	Study day 84
Month 4[1]	Study day 85	Study day 112
Month 5[1]	Study day 113	Study day 140
Month 6[1]	Study day 141	Earliest of (Study day 168 and day before study treatment stop date)

[1] The denominator for baseline and monthly mean scores is the number of days with a non-missing score; this is also used to determine whether or not a baseline (>=4 days) or monthly mean (>=10 days) is calculated.

EXACT PRO

- The EXACT-PRO (Evidera, 2016a) is a 14-item daily diary (typically completed at bedtime)
- The daily E-RS: COPD total score (and subscales) will be computed according to the E-RS in COPD user manual (Evidera, 2016b).
- The monthly mean for E-RS: COPD total score, and the subscale scores RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms will be calculated as the mean of the daily scores in the monthly intervals defined above.
- Mean monthly score = (sum of daily scores/# diary days completed).
- A participant must have at least 10 days of diary data in any month to contribute a non-missing monthly mean of daily values; otherwise the monthly mean for that month will be considered missing.
- A participant must have at least 4 days of diary data in the 7 days prior to treatment start date to contribute a non-missing mean of daily values for baseline; otherwise baseline will be considered missing.
- If missing values occur for individual items, the E-RS: COPD total score and E-RS: COPD subscale

Daily eDiary endpoints
score that contain the item will be set to missing on that day.
Responders according to E-RS: COPD Total and Subscale Scores
• A participant will be considered as a responder according to E-RS: COPD total score if their monthly mean change from baseline E-RS: COPD total score ≤ -2.0. • A participant will be considered as a non-responder according to E-RS: COPD total score if their monthly mean change from baseline E-RS: COPD total score >-2.0. • A participant will be considered as a responder according to E=RS: COPD breathlessness score if their month mean change from baseline E-RS: COPD breathlessness score ≤ -1.0. • A participant will be considered as a non-responder according to E-RS: COPD breathlessness score if their monthly mean change from baseline E-RS: COPD breathlessness score >-1.0. • A participant will be considered as a responder according to E-RS: COPD cough & sputum score if their monthly mean change from baseline E-RS: COPD cough & sputum score ≤ -0.70. • A participant will be considered as a non-responder according to E-RS: COPD cough & sputum score if their monthly mean change from baseline E-RS: COPD cough & sputum score >-0.70. • A participant will be considered as a responder according to E-RS: COPD chest symptoms score if their monthly mean change from baseline E-RS: COPD chest symptoms score ≤ -0.70. • A participant will be considered as a non-responder according to E-RS: COPD chest symptoms score if their monthly mean change from baseline E-RS: COPD chest symptoms score >-0.70. • If the monthly mean E-RS: COPD score is missing then response status will be missing.
Season
• For each participant and each month, season will be assigned based on the first date with a non-missing daily score in the monthly mean E-RS: COPD total score. • Australia will add 6 months to the first day of the monthly mean E-RS: COPD total score before season is assigned. • If the month of the first day of the monthly mean score period is: ▪ Dec, Jan or Feb then season is Winter ▪ Mar, Apr or May then season is Spring ▪ Jun, Jul or Aug then season is Summer ▪ Sep, Oct or Nov then season is Fall
Mean Number of Rescue Puffs per Day and Percentage Rescue Free Days
• If a participant has more than one daily diary record for any given day, the worst case response on that day for each endpoint will be used in the summaries and analyses. i.e. the maximum number of puffs of rescue use reported will be counted for the day in question and used to determine if it was a recue-free day. • A rescue-free day is defined as a day where the total puffs is 0. • For each summary period, the mean number of puffs per day and the percentage of rescue free days, will be calculated, using the number of days with non-missing values for the endpoint as denominator. • Rescue use will be summarized over the periods defined above.

HCRU Exacerbations
Duration
• The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1).
Severity
• Each HCRU exacerbation will be categorized based on severity as follows: o Mild: no treatment with oral/systemic corticosteroids and/or antibiotics and not involving hospitalisation, an emergency room visit or resulting in death o Moderate: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation, an emergency room visit or resulting in death). o Severe: required in-patient hospitalization, an emergency room visit, or resulted in death
Time to First Exacerbation
• The time to first on-treatment Moderate/Severe HCRU exacerbation will be calculated as exacerbation onset date of first on-treatment moderate or severe on-treatment exacerbation – date of start of treatment +1 • Participants will be represented from their treatment start date to their first on-treatment moderate or severe exacerbation or date of censoring. • For the strategic interim analysis, participants that have not experienced an on-treatment exacerbation are censored at the earliest of (treatment stop date + 3, date of death, or the interim cut-off date, 1AUG2018). • For the final analysis, participants that have not experienced an on-treatment exacerbation are censored at the earliest of (treatment stop date + 3, date of death, date of exclusion from the per protocol population (if analysis is in Per Protocol population))
Raw Annual Rate
• Raw annual rate is the event rate per 1000 participant-years, calculated as the number of events x 1000, divided by the total duration at risk (minimum(treatment stop date + 1, date of death, date of exclusion from the per protocol population (if analysis is in Per Protocol population)) – treatment start date + 1).
Offset Variable
• For analyses of exacerbation rate, the offset variable will be defined as the logarithm of the ((minimum (date of end of study treatment + 3, date of death, date of exclusion from the per protocol population (if analysis is in Per Protocol population)) – date of start of treatment + 1)/365.25)

EXACT Events
General
• The daily EXACT-PRO scores will be computed according to the EXACT-PRO user manual (Evidera, 2016a) and used to identify EXACT-defined events, including the frequency, duration and severity of the events. • Events will be categorized as recovered, censored, or persistent worsening (according to the manual).
Time to First Event
• The time to first on-treatment EXACT event will be calculated as the onset date of the first on-treatment EXACT event – date of start of treatment +1 • Participants will be represented from their treatment start date to their first EXACT event or date of censoring. • For the final analysis, participants that have not experienced an EXACT event are censored at the earliest of (Day 168, treatment stop date - 1, date of death, or date of final EXACT-PRO assessment, date of exclusion from the per protocol population (if analysis is in Per Protocol population))

Raw Annual Rate
• Raw annual rate is the event rate per 1000 participant-years, calculated as the total number of EXACT-defined events x 1000, divided by the total duration at risk (minimum(Day 168, treatment stop date - 1, date of death, date of final EXACT-PRO assessment, date of exclusion from the per protocol population (if analysis is in Per Protocol population)) – treatment start date + 1).
Offset Variable
• For analyses of EXACT event rate, the offset variable will be defined as the logarithm of the ((minimum (Day 168, treatment stop date - 1, date of death, date of final EXACT-PRO assessment, date of exclusion from the per protocol population (if analysis is in Per Protocol population)) – date of start of treatment + 1)/365.25)

CAT
CAT Score
• The CAT consists of eight items each formatted as a six-point differential scale: 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores on the eight items. The score can have values ranging from 0 to 40. • If one item is missing, then the score for that item is set as the average of the non-missing items. If more than one item is missing, then the CAT score will be set to missing. • If the language of the CAT conducted at a post-baseline visit is different to the language used at baseline, the CAT score for that visit and all subsequent visits will be set to missing. • If there is more than one response to a question at a visit or duplicate questionnaires, the CAT score for that visit will be set to missing.
Responders according to CAT Score
• A participant will be considered as a responder according to CAT score if their change from baseline CAT score ≤ -2.0. • A participant will be considered as a non-responder according to CAT score if their change from baseline CAT score >-2.0. • If CAT score is missing at a visit, the response status will be missing at that visit.
Season
• For each participant and each visit, season will be assigned based on visit date. • Australia will add 6 months to the visit date before season is assigned. • If the month of the visit is: ▪ Dec, Jan or Feb then season is Winter ▪ Mar, Apr or May then season is Spring ▪ Jun, Jul or Aug then season is Summer ▪ Sep, Oct or Nov then season is Fall

SGRQ
SGRQ Domain and Total Scores
• The SGRQ-C contains 14 questions with a total of 40 items grouped into three domains (Symptoms, Activity and Impacts). • Details for how to score the SGRQ-C, including handling of missing data or multiple responses to questions, are outlined in the SGRQ-C manual (Jones, 2016). • SGRQ-C domains and total scores will be converted to SGRQ scores as described in the manual. • Changes from baseline in domain and total score will be calculated for the converted scores. • If the language of the SGRQ-C conducted at a post-baseline visit is different to the language used at baseline, all SGRQ scores at that visit and all subsequent visits will be set to missing.

Responders according to SGRQ Total Score

- A participant will be considered as a responder according to SGRQ total score if their change from baseline SGRQ total score ≤ -4.0.
- A participant will be considered as a non-responder according to SGRQ total score if their change from baseline SGRQ total score >-4.0.
- If SGRQ total score is missing at a visit, the response status will be missing at that visit.
- Change from baseline SGRQ total score will be rounded to 1dp prior to assigning responder status.

Rescue Use via Sensor

Mean Number of Occasions and Percentage Rescue Free Days via Sensor

- The mean number of occasions of rescue per day and the percentage of rescue-free days will be calculated over the same time periods and using the same assumptions as rescue use via diary.
- Rescue-free Days - days within the diary data collection period with no recorded rescue inhaler usage by the sensor will be assigned a rescue inhaler usage of 0.

PROactive

General

- A PROactive Total Score and two domain scores (amount and difficulty) are derived using data from the C-PPAC questionnaire and a physical activity monitor worn for 7 days prior to the questionnaire.
- To derive the PROactive score at each visit the following is required:
    - Response to valid (i.e., no missing items) C-PPAC questionnaire
    - Median values of steps/day and VMU/min on at least 3 days of the 7 days prior to the C-PPAC questionnaire with >=8 hours wearing (the 3 days do not need to be consecutive).
- The C-PPAC questionnaire contains 14 items (12 questions and 2 scores from the activity monitor outputs) each scored from 0 to 4.
- The amount domain is calculated using 2 items from the C-PPAC questionnaire (amount of walking outside and chores outside) and 2 activity monitor outputs (vector magnitude units per minute (VMU/min) and steps/day).
- The difficulty domain is calculated using 10 items from the C-PPAC questionnaire.
- Each domain score is based on the addition of items (0-15 for amount and 0-40 for difficulty) and then scaled from 0-100.
- The total score is calculated as (amount+difficulty)/2
- Further details for how to score and scale the domain and total scores are outlined in the IMI PROactive user guide (14JUN16).

14.6.4. Safety

Adverse Events
AEs of Special Interest
• AESI are defined as events in the 'Infective pneumonia' SMQ in the MedDRA version current at the time of reporting. • Subjects receiving ICS (RMC - Corticosteroid – Inhaled) for at least 7 days at the time of Pneumonia onset.

Maximum/Minimum Post-Baseline and Worst-Case Post-Baseline	
Definition	**Reporting Details**
Maximum post-baseline (QTcF, QTc B, PR interval, ECG heart rate, pulse rate, systolic BP, diastolic BP and laboratory tests)	Change from baseline of maximum value over all time-points after Day 1
Minimum post-baseline (Diastolic BP and laboratory tests that do not have a lower limit = 0)	Change from baseline of minimum value over all time-points after Day 1
Worst case post-baseline (ECG findings)	• 'Abnormal' if any on-treatment assessment is evaluated as 'Abnormal' • 'Unable to evaluate' if all on-treatment assessments are 'Unable to evaluate' • 'Normal' if any on-treatment assessment is evaluated as 'Normal' and there are no on-treatment assessments evaluated as 'Abnormal'

NOTES :

- The treatment phase definitions specified in Section 14.4.1.4 will be used and only assessments within the on-treatment period will be considered in assessment of minimum/maximum/worst-case post-baseline.
- Assessment of minimum/maximum/worst-case post-baseline will include on-treatment data from scheduled, unscheduled and study treatment discontinuation visits (if applicable)

Laboratory Parameters
General
• NQ laboratory results will be treated as missing in summary displays. However, the results will be listed as received (e.g. '<x' or '>x'). • If numeric laboratory results are missing but a character result has been recorded, ie. <X, (the numeric part of the character value)/2 will be used to assign the PCI ranges. • A 'worst case post-baseline' change classification will be derived, in which participants will be counted in the 'to low' and 'to high' categories if they reported a change from an 'in range' baseline to a value below or above the PCI criteria (respectively) at any scheduled or unscheduled on-treatment visit. Participants who did not report a change to a value outside the PCI criteria at any visit after the start of study treatment will be counted in the 'to w/in range or no change' category.
Multiple Measurements for On-Treatment Visits for Safety
• Participants having both high and low values relative to PCI criteria at post-baseline visits for safety parameters will be counted in both the high and low categories of the "worst case post-baseline" row of related summary tables.

ECG

General

- The QTc data was collected via machine derived values (QTCB/QTCF) or manually derived values (QTCBC/QTCFC). For the purposes of reporting the following variable should be combined:
  - Combine QTCF with QTCFC
- If both QTCF and QTCFC are missing (and QT and RR are non-missing then the QTcF interval will be derived as follows:
  - QTcF interval (msec) = QT/[(RR/1000)**(1/3)]
  - If RR interval is not collected and the corrected QT interval by Bazett's method (QTcB) is collected, then RR interval (msec) will be derived prior to deriving QTcF as follows: RR interval (msec) = 1000*[(QT/QTcB)**2]
- If QTcF intervals are collected they will not be rederived.

ECG Categories

Maximum and maximum increase in d QTcF values will be reported in categories as below. In subjects who have QTc above 450 at baseline, decreases that result in a QTc that remains above 450 will be considered No Change.

ECG Parameter	Units	Category
Absolute		
Absolute QTcF Interval	msec	No Change or Decrease to <=450
		Increase To >450 to <=480
		Increase To >480 to <=500
		Increase To >500
Change from Baseline		
Change from Baseline QTcF	msec	Increase of <=30 ms
		Increase of 31-60 msec
		Increase of >60 msec

Assessment of maximum post-baseline will include on-treatment data from scheduled, unscheduled and study treatment discontinuation visits (if applicable)

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as completion of all phases of the study including the last study visit and the last scheduled procedure shown in the Schedule of Activities (Appendix 2). • For the purposes of reporting, a participant is considered to have completed the study if they have not withdrawn and attended Visit 10. • Withdrawn participants were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Data from the Early Withdrawal visit will not be included in any summaries or analyses except as part of a worst case post-baseline assessment.

14.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a “blank” in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Outliers	• If outliers are identified, analyses may be repeated excluding the outlying data. • Any participants/data excluded from summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values

The following table identifies a range of potential clinical importance (PCI) for each laboratory analyte. Limits with an 'x' are multipliers of the central laboratory normal range. Values above and below this range will be considered of PCI.

Hematology Analyte (units)	Effect	COPD Patients	
		Low	High
Platelet Count ($x10^9$/L)		0.90x	1.10x
Red Blood Cell Count ($x10^{12}$/L)		0.93x	1.07x
White Blood Cell Count ($x10^9$/L)		0.70x	1.60x
Reticulocyte Count (%)			>4%
Hemoglobin (g/L)	Males	0.85x	1.20x
	Females	0.85x	1.20x
Hematocrit (Ratio of 1)	Males	0.50x	1.30x
	Females	0.50x	1.30x
MCV (fL)		0.25x	2.00x
MCH (pg)		0.85x	1.20x
MCHC (g/dL)		0.85x	1.10x
Neutrophils (%)		0.65x	1.50x
Lymphocytes (%)		0.80x	1.20x
Monocytes (%)		0.80x	1.60x
Eosinophils (%)			2.00x
Basophils (%)			5.00x

Note: Multipliers are identified by "x", otherwise actual comparison values are provided with units.

Chemistry Analyte	Effect	COPD Patients	
		Low	High
BUN (mmol/L)		0.70x	1.60x
Creatinine (μmol/L)			1.30x (or >27 μmol/L increase from baseline)
Glucose fasting (mmol/L)		<0.6x	>4x
Sodium (mmol/L)		0.80x	1.15x
Potassium (mmol/L)		0.75x	1.30x
Chloride (mmol/L)		0.90x	1.10x
Bicarbonate (mmol/L)		<18 mmol/L	>32 mmol/L
Calcium (mmol/L)		0.85x	1.08x
GGT (U/L)		0.85x	1.10x
Uric Acid (mg/dL)	Males	<2.1 mg/dL	>8.5 mg/dL
	Females	<2.0 mg/dL	>7.0 mg/dL
Albumin (mmol/L)		0.90x	1.50x
Total Protein (mg/dL)			1.25x

Note: Multipliers are identified by "x", otherwise actual comparison values are provided with units.

Liver Function Test Analyte	Effect	PCI Range	Unit
ALT/SGPT	High	≥ 3x ULN	U/L
AST/SGOT	High	≥ 3x ULN	U/L
Alkaline Phosphatase	High	≥ 2x ULN	U/L
Total Bilirubin	High	≥ 2x ULN	μmol/L
Direct Bilirubin	High	≥ 2x ULN	μmol/L
Total Bilirubin + ALT	High	≥ 2x ULN Total Billirubin + ≥ 3x ULN ALT	μmol/L U/L

14.8.2. ECG

ECG Parameter	PCI Range	Unit
Absolute QTc Interval (QTcB, QTcF)	>530	msec
Increase from Baseline QTc	>60	msec
QT Interval	<300 or >500	msec
PR Interval	<120 or >240	msec
QRS Interval	<70 or >125	msec
RR Interval	<375 or >1714	msec
Heart Rate	<35 or >120	bpm

14.8.3. Vital Signs

Vital Sign Parameter	PCI Range	Unit
Systolic BP	<90 or >160	mmHg
Diastolic BP	<40 or >110	mmHg
Heart Rate	<35 or >120	bpm
Respiration Rate	<8 or >30	breaths /min

14.9. Appendix 9: Population Pharmacokinetic Analyses

14.9.1. Population Pharmacokinetic Dataset Specification

14.9.1.1. Handling Missing Demographic and Covariate Data

Missing demographic and covariate data will not be imputed.

14.9.1.2. Handling Missing Dose Times

Missing dose time information will be handled on a case by case basis by imputing this information based on prior dosing times or based on recorded PK collection times. The details of these imputations will be described in the report.

14.9.1.3. Handling Missing Times of PK Samples

Missing times for PK will be handled on a case by case basis by imputing this information based on the dose time and/or times of other PK. The details of these imputations will be described in the report.

14.9.1.4. Handling of PK Data Below the Lower Limit of Quantification

Any PK data below the lower limit of quantification will be set to missing.

14.9.1.5. Dataset Specification

General description and rules:

- Missing or unknown values in covariates, if not to be imputed, will be assigned -99.
- The dataset is sorted by STUD, SUBJID, DATE, RTFD, EVID descending.
- The data items (columns) in the analysis-ready data file will be provided in the same order as follows.
- NQ concentration values will be included as detailed for the CONC variable.
- Non-numerical concentration values (such as NS, NR, NA) will not be included.
- Placebo participants will not be included.
- The dataset will be a comma delimited ASCII text file and will be named:
    - NM.*compound.study*.PK.v1.csv
    - Where “compound” is the compound name (e.g. GSK1234567) and “study” is the study number (e.g. 205724).

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
ID	NONMEM participant identifier	Integer	None	Never	Sequential participant identifier across study after data is sorted by STUD, SUBJID, DATE, RTFD, EVID. Numbering to start at 1. To be entered in all rows for each participant.
STUDYID	Unique identifier for a study	Char	None	Never	205724 for all records
STUD	Study ID	Num	None	Never	205724 for all records
SUBJID	Participant identifier for study	Num	None	Never	Participant identifier, which must be unique within the study. The identification number of the participant as recorded on the CRF. Exclude placebo participants. Include participants who have received IP and have at least one measurable drug concentration. To be entered in all rows for each participant.
COUNTRY	Country	Char	None	Never	Country of the investigational site in which the participant participated in the trial; e.g. USA. To be entered in all rows for each participant.
SITEID	Unique identifier for a study site	Char	None	Never	e.g. PPD any lead zero should not be included. To be entered in all rows for each participant.
CONC	Drug Concentration	Num	ng/mL	*Never*	CONC=0 for DOSE_GSK1325756 records. No sample (NS), insufficient sample (IS) and no result (NR) records will be excluded from dataset. CONC='.' for PK_GSK1325756 records < LOQ (i.e. if drug conc is NQ).
LNCONC	Natural log of CONC column	Num	ng/mL	Never	Natural log of CONC column. If CONC=0, then LNCONC='.'.
LLQ	Lower Limit of quantification	Num	ng/mL	Never	LLQ=5 or from source data if different. To be entered in all rows for each participant.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
LNLLQ	Natural log of LLQ column	Num	ng/mL	Never	Natural log of LLQ column. If LLQ=0, then LNLLQ='.'.
MATRIX	Sample matrix	Num	None	Never	MATRIX=1 (blood).
MATRTEXT	Sample matrix text	Char	None	Never	Text corresponding to code for MATRIX. Enter 'Blood' for all rows.
LABL	Label describing the record	Char	None	Never	LABL explains the type of measurement for CONC for the current record. LABL=DOSE_GSK1325756 for dose record. LABL=PK_GSK1325756 for blood concentration record.
DATE	Date of Record	MM/DD/YYYY	None	Never	Date of record.
DATETIME	Date and time of record	MM/DD/YYYY HH:MM:SS	None	Never	Date and time of record.
DAY	Study day number of record	Num	None	Never	Day of study relative to first IP dose.
NDAY	Nominal day	Num	day	Never	Schedule visit day of study relative to first IP dose.
NOMT	Nominal time since FIRST IP dose	Num	h	Never	Nominal time of study relative to first IP dose. NOMT=0 for first dosing record only.
NOMTLD	Nominal time since latest IP dose	Num	h	Never	Nominal time of study relative to last IP dose prior to sample. NOMTLD=0 for dosing records.
RTFD	Relative time from FIRST IP dose	Num	h	Never	Actual time from FIRST dose of IP.
RTLD	Relative time from latest IP dose	Num	h	Never	Actual time from last dose of IP prior to sample. When LABL=DOSE_GSK1325756, RTLD=0. For pre-dose PK sample Visit 6, 7 and 10, RTLD is relative to the previous dose.
DOSE	Dose amount	Num	mg	Never	DOSE=5, 10, 25, 35 or 50 per treatment administered. To be entered in all rows for each participant.
DRUG	Name of drug	Char	None	Never	DRUG=GSK1325756. To be entered in all rows for each participant.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
REG	Dosing Regimen	Integer	None	Never	REG=2 for BD. To be entered in all rows for each participant.
REGTEXT	Participant dose regimen text	Char	None	Never	REGTXT=BD, text corresponding to code for REG. To be entered in all rows for each participant.
ROUT	Route of administration	Integer	None	Never	ROUT=1 for PO. To be entered in all rows for each participant.
ROUTTEXT	Participant route of administration text	Char	None	Never	ROUTTEXT=PO, text corresponding to code for ROUT. To be entered in all rows for each participant.
CNC	NONMEM Country code	Integer	None	Never	Australia, Canada, Germany, Korea, Netherlands, Poland, Romania, Spain, US. Assign integer as appropriate for each country. Eg. 1=US To be entered in all rows for each participant.
CMT	NONMEM Compartment code	Integer	None	Never	CMT=1 for DOSE_GSK1325756 records. CMT=2 for PK_GSK1325756 records.
EVID	NONMEM Event ID	Integer	None	Never	EVID=1 for LABL= DOSE_GSK1325756. EVID=0 for LABL= PK_GSK1325756.
AMT	NONMEM Amount of drug administered	Num	mg	Never	AMT=0 for LABL= PK_GSK1325756 records. AMT=5, 10, 25, 35 or 50 (ass appropriate) for LABL= DOSE_GSK1325756 records.
II	NONMEM Inter-dose interval	Integer	h	Never	II=0 for LABL= PK_GSK1325756. II=12 for LABL= DOSE_GSK1325756, except II=0 for LABL= DOSE_GSK1325756 on Day 1 only.
SS	Steady-state data item	Integer	None	Never	SS=0 for LABL= PK_GSK1325756 records. SS=1 for LABL= DOSE_GSK1325756 records, except SS=0 for LABL= DOSE_GSK1325756 records on Day 1 only.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
RATE	NONMEM Rate of drug infusion	Integer	None	Never	RATE=0 for LABL= PK_GSK1325756 records. RATE=-2 for LABL= DOSE_GSK1325756 records.
MDV	NONMEM Missing data value	Integer	None	Never	MDV=1 for LABL= DOSE_GSK1325756 records. MDV=0 for LABL= PK_GSK1325756 records. MDV=1 for LABL= PK_GSK1325756 records < LOQ (NQ).
VIS	Visit number	Integer	None	Never	From source data.
POP	Population	Integer	None	Never	POP=1, for COPD. To be entered in all rows for each participant.
POPTEXT	Participant population text	Char	None	Never	POPTEXT=COPD, text corresponding to code for POP. To be entered in all rows for each participant.
COH	Cohort	Integer	None	Never	COH=1. To be entered in all rows for each participant.
AGE	Participant Age	Integer	year	If missing impute with -99	From source data. To be entered in all rows for each participant.
SEX	Participant gender	Integer	None	Never	0=Male, 1=Female To be entered in all rows for each participant.
SEXTEXT	Participant gender text	Char	None	Never	Text corresponding to code for SEX, e.g. MALE or FEMALE). To be entered in all rows for each participant.
BMI	Baseline Body Mass Index	Num	kg/m^2	If missing impute with -99	Ensure consistent with S&P formula. E.g. Formula: Weight(kg)/(height(m)**2) To be entered in all rows for each participant.
BSA	Baseline Body Surface Area	Num	m^2	If missing impute with -99	Formula: BSA (m^2) = 0.024265 • Height(cm)$^{0.3964}$ • Weight(kg)$^{0.5378}$ Ensure consistent to with S&P formula. To be entered in all rows for each participant.
WT	Baseline Participant weight	Num	kg	If missing impute with -99	From source data. To be entered in all rows for each participant.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
HT	Baseline Participant height	Num	m	If missing impute with -99	From source data. To be entered in all rows for each participant.
RACE1	Participant race code1	Integer	None	Never	From source data e.g. 1=African American / African Heritage 2=American Indian or Alaska Native 3=Asian – Central / South Asian Heritage 4=Asian – East Asian Heritage 5=Asian – Japanese Heritage 6=Asian – South East Asian Heritage 7=Asian – Mixed Race 8=Native Hawaiian or other Pacific Islander 9=White – Arabic / North African Heritage 10=White – White / Caucasian / European Heritage 11=White – Mixed Race 12=Mixed Race To be entered in all rows for each participant.
RACE1TXT	Participant race 1 text	Char	None	Never	Text corresponding to code for RACE1 To be entered in all rows for each participant.
RACE2	Participant race code2	Integer	None	Never	1=East Asian: Asian – East Asian Heritage & Asian – Japanese Heritage 2=White: White – Arabic / North African Heritage White – White / Caucasian / European Heritage 3=African: African American / African Heritage; 4=Other: American Indian or Alaska Native; Asian – Central / South Asian Heritage; Asian – South East Asian Heritage; Asian – Mixed Race; Native Hawaiian or other Pacific Islander; White – Mixed Race & Mixed Race To be entered in all rows for each participant.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
RACE2TXT	Participant race 2 text	Char	None	Never	Text corresponding to code for RACE2 To be entered in all rows for each participant.
ETHN	Participant ethnicity	Num	None	Never	From source data definition. E.g 1=Hispanic or Latino, 2=Non-Hispanic To be entered in all rows for each participant.
ETHNTEXT	Participant ethnicity text	Char	None	Never	Text corresponding to code for ETHN. To be entered in all rows for each participant.
REGN	Region for participant	Num	None	Never	1 = East Asia (to include Japan, South Korea and Taiwan) 2 = Rest of the World (to include all other countries) To be entered in all rows for each participant.
SMOK	Participant smoking status	Integer	None	Never	0=Non-smoker, 1=Smoker, 2=Former smoker To be entered in all rows for each participant.
SMOKTEXT	Participant smoking status text	Char	None	Never	Text corresponding to code for SMOK. To be entered in all rows for each participant.
CMED1	COPD conmeds identifier	Num	None	Never	0 = no concomitant use 1 = intermittent use 2 = continuous use To be entered in all rows for each participant.
CMED1TXT	Participant CMED1 text	Char	None	Never	Text corresponding to code for CMED1. To be entered in all rows for each participant.
CRCL	Baseline Creatinine Clearance	Num	mL/min	If missing impute with -99	From source data. OR Specify appropriate formula e.g. Creatinine Clearance will be calculated based on the Cockcroft-Gault equation. • CrCL (ml/min) = [140 – AGE (in years)]*Weight(kg)*0.85 (for female particpants) /

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
					[72* Serum Creatinine (micromol/L) * 0.0113 • CrCL (mL/min) = (140 – Age (yr)) * IBW (kg) / (72 • SCr (µmol/L) * 0.0113) * [0.85 if female], where IBW (kg) = 50 (kg) [- 4.5 (kg) if female]+ 2.3 (kg) * (HT (inch) - 60) • Delete one as appropriate and ensure consistency with S&P formula • To be entered in all rows for each participant.
CMED2	Gastric acid reducing conmeds identifier	Num	None	Never	0 = no concomitant use 1 = intermittent use 2 = continuous use To be entered in all rows for each participant.
CMED2TXT	Participant CMED2 text	Char	None	Never	Text corresponding to code for CMED2. To be entered in all rows for each participant.
CMED3	Identifier for on-treatment gastric acid increasing concomitant medication	Num	None	Never	0 = no concomitant use 1 = intermittent use 2 = continuous use To be entered in all rows for each participant.
CMED3TXT	Participant concomitant medication text	Char	None	Never	Text corresponding to code for CMED3. To be entered in all rows for each participant.
CMED4	P-gp inhibitor conmeds identifier	Num	None	Never	0 = no concomitant use 1 = intermittent use 2 = continuous use To be entered in all rows for each participant.
CMED4TXT	Participant CMED4 text	Char	None	Never	Text corresponding to code for CMED4. To be entered in all rows for each participant.
CMED5	Identifier for on-treatment p-gp inducer concomitant medication	Num	None	Never	0 = no concomitant use 1 = intermittent use 2 = continuous use To be entered in all rows for each participant.

Variable	Label (Variable description)	Type	Units	Missing value	Codes/Derivation/Notes
CMED5TXT	Participant concomitant medication text	Char	None	Never	Text corresponding to code for CMED5. To be entered in all rows for each participant.
ALB	Baseline Albumin	Num	Specify	If missing impute with -99	Baseline defined in the source dataset To be entered in all rows for each participant.
TBIL	Baseline Total bilirubin	Num	Specify	If missing impute with -99	Baseline defined in the source dataset To be entered in all rows for each participant.
TFIB	Baseline Fibrinogen	Num	Specify	If missing impute with -99	Baseline defined in the source dataset To be entered in all rows for each participant.

Current Therapies for COPD: CMED1

Therapy	Efficacy Claims	Main Safety Concerns
Long-acting β_2-agonists (LABAs)		
Formoterol Indacaterol Salmeterol Olodaterol	Bronchodilator treatment to relieve symptoms in patients with COPD. Not used alone, generally in combination with inhaled corticosteroids and LAMAs.	Adverse reactions related to β receptor agonist pharmacology *e.g.* tremor, tachycardia, hypokalaemia, hyperglycaemia. Use of indacaterol has been associated with post-inhalation cough. Hypersensitivity reactions can occur with ICS, LAMA and LABAs, but are unlikely to affect the majority of patients. Cardiovascular effects have also been associated with use of muscarinic antagonists and β_2 agonists in patients with COPD.

Therapy	Efficacy Claims	Main Safety Concerns
Long acting anti-muscarinic antagonists (LAMAs)		
Tiotropium Aclidinium Bromide Glycopyrronium bromide Umeclidinium	Bronchodilator treatment to relieve symptoms in patients with COPD. Same as above.	Adverse reactions related to anti-muscarinic pharmacology. The most commonly reported adverse effects include dry mouth, GI effects and upper respiratory system infection. Hypersensitivity reactions can occur with ICS, LAMA and LABAs, but are unlikely to affect the majority of patients Cardiovascular effects have also been associated with use of muscarinic antagonists and β_2 agonists in patients with COPD.
Long acting combination bronchodilators		
Albuterol/ipratropium bromide Vilanterol/umeclidinium Olodaterol/tiotropium Indacaterol/glycopyrrolate Formoterol/glycopyrrolate Formoterol/aclidinium	Bronchodilator treatment superior to LABA or LAMA alone relieving symptoms in patients with COPD.	Adverse reactions related to β receptor agonist and anti-muscarinic pharmacology
Methylxanthines		
Theophylline Aminophylline	Bronchodilator effects and claimed anti-inflammatory effects.	Dose-related toxicity including the development of atrial and ventricular arrhythmias and grand mal seizures.
Inhaled glucocorticosteroids		
Beclomethasone Budesonide Fluticasone propionate Fluticasone furoate Mometasone	Anti-inflammatory effects; normally used in combination with LAMAs and LABAs	The class effects of inhaled corticosteroids can include oral candidiasis, hoarse voice, skin bruising and increased risk of pneumonia. Systemic corticosteroid class effects including hypothalamic-pituitary-adrenal (HPA) axis suppression, decrease in bone mineral density and ocular disorders (*e.g.* glaucoma and cataracts). Pneumonia is a recognized class

Therapy	Efficacy Claims	Main Safety Concerns
		risk with the use of inhaled corticosteroid (ICS) in COPD [Spencer, 2011; Drummond, 2008], however, the benefit of ICS continue to outweigh the risks [EMA, 2016] Hypersensitivity reactions can occur with ICS, LAMA and LABAs, but are unlikely to affect the majority of patients.
Inhaled glucocorticosteroids (ICS, in combination with inhaled bronchodilators)		
Formoterol/budesonide Salmeterol/Fluticasone propionate Vilanterol/Fluticasone Furoate Formoterol/beclomethasone Formoterol/mometasone	An inhaled corticosteroid combined with a LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status.	As described for LABAs and inhaled glucocorticosteriods above. Crim et al. (2015) pneumonia was shown to be more frequent in patients who received fluticasone/vilanterol than those who received vilanterol alone.
Inhaled glucocorticosteroids (ICS, in combination with inhaled LABA and LAMA)		
Fluticasone Furoate/Umeclidium/Vilanterol	Adding a LAMA to existing LABA/ICS improves lung function and patient reported outcomes in particular, exacerbation risk.	As described for LABAs, LAMAs and inhaled corticosteroids above.
Phospodiesterase-4 inhibitors		
Roflumilast	Reduction of exacerbations in patients with severe COPD. Modest improvement in FEV1 (versus placebo) and small improvements in SCRQ and COPD-related systems. No significant changes in exercise tolerance with PDE4 inhibitors. Unclear benefit on modifying FEV1 decline, hospitalization or mortality in COPD. [Chong J et al. 2013].	Weight loss, abdominal pain, diarrhoea, nausea, headache and sleep disturbances. Caution for use is advised in patients with depression.

Therapy	Efficacy Claims	Main Safety Concerns
Antibiotics		
Macrolides (e.g. azithromycin, erythromycin)	Regular use of may reduce exacerbation rate. Azithromycin or erythromycin for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.	Azithromycin use associated with increased incidence of bacterial resistance and impaired hearing.

CMED2: Gastric acid reducing conmeds

Obs	VAR1	VAR2
1	Term Name	Code
2	ESOMEPRAZOLE MAGNESIUM	1479302
3	PEPTAZOL (NOS)	59841501
4	DOMPERIDONE MALEATE + RABEPRAZOLE SODIUM	54702201
5	CLARITHROMYCIN + LANSOPRAZOLE	54953101
6	PANTOPRAZOLE	1263201
7	ESOMEPRAZOLE	1479301
8	DOMPERIDONE + PANTOPRAZOLE	53545101
9	ZEGERID (NOS)	54613401
10	LANSOPRAZOLE SODIUM	1159002
11	ESOMEPRAZOLE STRONTIUM	1479304
12	ESOGARD (NOS)	59864501
13	OMEPRAZOLE MAGNESIUM	661203
14	ZOLTUM (NOS)	59177101
15	TENATOPRAZOLE	1401301
16	PRAZOL (NOS)	51163801
17	DEXLANSOPRAZOLE	53869001
18	DOMPERIDONE + RABEPRAZOLE	53611501
19	DOMPERIDONE + OMEPRAZOLE	53773301
20	CLARITHROMYCIN + LANSOPRAZOLE + TINIDAZOLE	53235701
21	LEVOSULPIRIDE + RABEPRAZOLE SODIUM	54347301
22	LEVOSULPIRIDE + RABEPRAZOLE	54342301
23	PROTON PUMP INHIBITOR NOS	53027601
24	IPP (NOS)	54019901
25	OMEPRAZOLE SODIUM	661202
26	PANTOPRAZOLE MAGNESIUM	1263203
27	ESOMEPRAZOLE SODIUM	1479303
28	DOMPERIDONE MALEATE + PANTOPRAZOLE SODIUM	54543201
29	PROTONIX (NOS)	54411301
30	GASTROZOL (NOS)	54724001
31	OMEPRAZOLE + SODIUM BICARBONATE	53827801
32	ALIMENTARY TRACT AND METABOLISM;DRUGS FOR	A02BC
33	LANSOPRAZOLE	1159001
34	MOSAPRIDE CITRATE + RABEPRAZOLE SODIUM	54691301
35	ESOMEPRAZOLE POTASSIUM	1479305

NDAY: For deriving the nominal day which is the planned day, DAY specific information is not available in EXPOSURE dataset. VISIT variable and the time and events table might have to be taken into account to find the exact plan of events.

NOMT: It is twice daily dosing with inter-dose interval given to be 12 hours. Therefore, to find the planned time of event since the first dose in hours, again the VISIT variable and time and events will have to be considered.

NOMTLD: In case of PK_GSK1325756 records, the planned time point variable will give the value of this variable for all the post-dose records. For the pre-dose records, this variable will have missing values since there is no fixed time point since the previous dose for pre-dose records.

RTFD: The time difference between the first dose of the subject and the current dose (when LABL=DOSE_GSK1325756) should be calculated in hours. The time difference between the first dose of the subject and the PK sample collection time (when LABL=PK_GSK1325756) should be calculated in hours.

RTLD: The latest dose prior to the PK sample collection time will have to be found out and the time difference between that dose and the PK sample collection time will be calculated in hours.

14.10. Appendix 10: Abbreviations & Trade Marks

14.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALLSUB	All Subjects
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
BD	Bronchodilator
BP	Blood Pressure
BUN	Blood urea nitrogen
C-PPAC	Clinical Visit PROactive Physical Activity in COPD
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CID	Clinically Important Deterioration
CMH	Chronic Mucus Hypersecretion
CrI	Credible Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
DBF	Database Freeze
DM	Data Management
DP	Decimal Places
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EW	Early Withdrawal
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FEV1	Forced Expiratory Volume in 1 Second
FUP	Functional Uniform Prior
FVC	Forced Vital Capacity
GGT	Gamma-glutamyl transferase
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HCRU	Healthcare Resource Utilization
IDSL	Integrated Data Standards Library
LS	Least Squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCSE	Monte Carlo Standard Error
MCV	Microtic cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat

Abbreviation	Description
MLE	Maximum likelihood estimate
MMRM	Mixed Model Repeated Measures
NQ	Non-quantifiable
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population PK
QC	Quality Control
RAP	Reporting & Analysis Plan
RMC	Respiratory Medication Class
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SDL	Source Data Lock
SDTM	Study Data Tabulation Model
SGOT	Serum glutamic oxalocaetic transaminase
SGPT	Siamane glutamate pyruvate transaminase
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SI	System Independent
SMQ	Standardized MedDRA Query
SRDP	Study Results Dissemination Plan
ULN	Upper limit of normal

14.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

14.11. Appendix 11: List of Data Displays

14.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Strategic Interim Statistical Analysis Complete		
Section	**Tables**	**Figures**
Study Population	1.1 to 1.20	
Efficacy	2.1 to 2.52	2.1 to 2.35
Conditional Efficacy		2.36 to 2.xx
Safety	3.1 to 3.23	3.1 to 3.6
Pharmacokinetic		
Pharmacokinetic / Pharmacodynamic		
Biomarker	6.1 to 6.2	6.1 to 6.2
Section	**Listings**	
ICH Listings	1 to 1	
Other Listings	2 to 2	
Final Statistical Analysis Complete (Including Post SAC)		
Section	**Tables**	**Figures**
Study Population	1.1 to 1.43	1.1
Efficacy	2.1 to 2.49	2.1 to 2.32
Conditional Efficacy		2.33 to 2.xx
Safety	3.1 to 3.37	3.1 to 3.11
Pharmacokinetic	4.1 to 4.8	4.1 to 4.13
Pharmacokinetic / Pharmacodynamic		5.1 to 5.4
Biomarker	6.1 to 6.4	6.1 to 6.4
Section	**Listings**	
ICH Listings	1 to 36	
Other Listings	37 to 69	

14.11.2. Deliverables

In all displays the term "Subjects" is used to refer to “Participants”.

Delivery [Priority]	Description
StInt	Strategic Interim Statistical Analysis Complete
SAC	Final Statistical Analysis Complete
Post SAC	Additional outputs provided after SAC

14.11.3. Study Population Tables

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Participant Disposition						
1.1	1.1	mITT	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT Include number of ongoing participants for strategic interim	StInt, SAC
	1.2	All Subjects	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
	1.3	All Subjects	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	SAC
1.2	1.4	mITT	NS1	Summary of Number of Subjects by Country and Site ID		StInt, SAC
1.3	1.5	PP	NS1	Summary of Number of Subjects by Country and Site ID		StInt, SAC
1.4	1.6	mITT		Summary of Attendance at Each Clinic Visit		StInt, SAC
Protocol Deviation						
	1.7	mITT	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
	1.8	All Subjects	IE2	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations for Screen or Run-in failures	Add a row “Number of Screen Failures” above “any criteria deviations”. Percentage will be based on number of screen failures	SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	1.9	mITT	IE1	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations for the Modified Intent-to-treat Population		SAC
Population Analysed						
1.5	1.10	All Subjects	SP1	Summary of Study Populations	IDSL Number of participants who were in the All Participants population, who were randomized, the number in the ITT population (Strategic interim only), the number in the mITT population. Of those in the mITT, the number and percentage of participants in the PP, Symptomatic (Strategic interim only), PK and PK2 populations	StInt, SAC
	1.11	mITT	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	SAC
Demographic and Baseline Characteristics						
1.6	1.12	mITT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	StInt, SAC
1.7	1.13	PP	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	StInt, SAC
	1.14	All Subjects	DM11	Summary of Age Ranges	EudraCT	SAC
	1.15	mITT	DM6	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	1.16	All Subjects	EMA Table 1	Summary of Number of Subjects Enrolled by Country	EMA Reporting Package. Macro: EMA_COUNTRY	SAC
	1.17	All Subjects	EMA Table 2	Summary of Number of Subjects Enrolled by Age Category	EMA Reporting Package. Macro: EMA_AGEGRP	SAC
1.8	1.18	mITT	SU1	Summary of Smoking History and Smoking Status at Screening	Include smoking status, smoking pack years, cigarettes smoked/day	StInt, SAC
1.9	1.19	PP	SU1	Summary of Smoking History and Smoking Status at Screening	Include smoking status, smoking pack years, cigarettes smoked/day	StInt, SAC
1.10		Symptomatic	SU1	Summary of Smoking History and Smoking Status at Screening	Include smoking status, smoking pack years, cigarettes smoked/day	StInt
	1.20	mITT	SP_T12	Summary of COPD History at Screening		SAC
1.11	1.21	mITT	SP_T13	Summary of HCRU Exacerbation History at Screening	See notes in Section 14.6.3	StInt, SAC
1.12	1.22	PP	SP_T13	Summary of HCRU Exacerbation History at Screening	See notes in Section 14.6.3	StInt, SAC
1.13	1.23	mITT		Summary of Screening Spirometry Measures	Pre-BD FEV1 (L), Post-BD FEV1 (L), Predicted normal FEV1 (L), Percent predicted normal post-BD FEV1 (%), Percent predicted normal post-BD FEV1: <50%, >=50%, Post-BD FVC (L), Post-BD FEV1/FVC	StInt, SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.14	1.24	PP		Summary of Screening Spirometry Measures	Pre-BD FEV1 (L), Post-BD FEV1 (L), Predicted normal FEV1 (L), Percent predicted normal post-BD FEV1 (%), Percent predicted normal post-BD FEV1: <50%, >=50%, Post-BD FVC (L), Post-BD FEV1/FVC	StInt, SAC
	1.25	mITT		Summary of GOLD Stages at Screening	GOLD 1-4 and GOLD A-D	SAC
1.15	1.26	mITT		Summary of Baseline Symptomatic Characteristics	Proportion of participants with CMH ± according to SGRQ, with baseline E-RS: COPD total score </>=10, with baseline CAT Score </>=10, with ICS+LABA+LAMA vs. ICS+LABA vs. LABA+LAMA vs. Other COPD medication	StInt, SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.16	1.27	PP		Summary of Baseline Symptomatic Characteristics	Proportion of participants with CMH ± according to SGRQ, with baseline E-RS: COPD total score </>=10, with baseline CAT Score </>=10, with ICS+LABA+LAMA vs. ICS+LABA vs. LABA+LAMA vs. Other COPD medication	StInt, SAC
Prior and Concomitant Medications						
	1.28	mITT	CM1	Summary of COPD Concomitant Medications Taken Pre-treatment	Use RMC instead of ATC Level 1	SAC
	1.29	mITT	CM1	Summary of COPD Concomitant Medications Taken On-Treatment, Medications Given for Reasons Other than an Exacerbation	Use RMC instead of ATC Level 1	SAC
	1.30	mITT	CM1	Summary of COPD Concomitant Medications Taken Post-treatment	Use RMC instead of ATC Level 1	SAC
	1.31	mITT	CM1	Summary of On-treatment COPD Concomitant Medications Given for an Exacerbation	Use RMC instead of ATC Level 1	SAC
1.17	1.32	mITT		Summary of COPD Concomitant Medication Combinations Taken at Screening	Number and percentage of participants taking each medication in the RMC combination defined in Section 14.6.2	StInt, SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.18	1.33	mITT		Summary of COPD Concomitant Medication Combinations Taken at Baseline	Number and percentage of participants taking each medication in the RMC combination defined in Section 14.6.2	StInt, SAC
1.19		Symptomatic		Summary of COPD Concomitant Medication Combinations Taken at Baseline	Number and percentage of participants taking each medication in the RMC combination defined in Section 14.6.2	StInt
	1.34	PP		Summary of COPD Concomitant Medication Combinations Taken at Month 6	Number and percentage of participants taking each medication in the RMC combination defined in Section 14.6.2 during Month 6	Post SAC
	1.35	mITT	CM1	Summary of On-treatment Non-COPD Concomitant Medications	Use ATC Level 1	SAC
	1.36	mITT	CM1	Summary of Post-treatment Non-COPD Concomitant Medications	Use ATC Level 1	SAC
Past and Current Medical History						
	1.37	mITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC
	1.38	mITT	MH4	Summary of Current Medical Conditions		SAC
	1.39	mITT	Table 1.23 Study GSK2834425/CTT116853	Summary of Cardiovascular History/Risk Factors		SAC

Study Population Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.20	1.40	mITT	FH1	Summary of Family History of Cardiovascular Risk Factors		StInt, SAC
Exposure and Treatment Compliance						
	1.41	mITT	IP1	Summary of Treatment Compliance		SAC
	1.42	mITT		Summary of Daily Diary Compliance		SAC
	1.43	mITT	EX1	Summary of Exposure to Study Treatment	ICH E3	SAC

14.11.4. Study Population Figures

Study Population Figures					
SAC No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disposition of Subjects					
1.1.	mITT		Kaplan-Meier Plot of Time to Study Withdrawal		SAC

14.11.5. Efficacy Tables

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
E-RS: COPD						
2.1	2.1	PP	PD4	Summary of Baseline E-RS: COPD Scores	Endpoints: E-RS: COPD total and subscale scores Include total column	StInt, SAC
2.2		Symptomatic	PD4	Summary of Baseline E-RS: COPD Scores	Endpoints: E-RS: COPD total and subscale scores Include total column	StInt
2.3	2.2	PP	PD4	Summary of Monthly Mean E-RS: COPD Scores	Endpoints: E-RS: COPD total and subscale scores Include raw and change from baseline scores for participants with non-missing E-RS data for each month	StInt, SAC
2.4		Symptomatic	PD4	Summary of Monthly Mean E-RS: COPD Scores	Endpoints: E-RS: COPD total and subscale scores Include raw and change from baseline scores for participants with non-missing E-RS data for each month	StInt
2.5	2.3	PP		Bayesian Dose Response Analysis of Change from Baseline E-RS: COPD Scores at Month 6	Endpoint: Month 6 E-RS: COPD total and subscale scores	StInt, SAC
2.6		Symptomatic		Bayesian Dose Response Analysis of Change from Baseline E-RS: COPD Total Score at Month 6	Endpoint: Month 6 E-RS: COPD total score	StInt

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.7	2.4	PP		Bayesian Analysis of Change from Baseline Monthly Mean E-RS: COPD Scores up to Month 6	Bayesian MMRM on Change from Baseline Endpoints: E-RS: COPD total and subscale scores	StInt, SAC
2.8		Symptomatic		Bayesian Analysis of Change from Baseline Monthly Mean E-RS: COPD Scores up to Month 6	Bayesian MMRM on Change from Baseline Endpoints: E-RS: COPD total and subscale scores	StInt
2.9		ITT		Bayesian Analysis of Change from Baseline Monthly Mean E-RS: COPD Scores up to Month 6	Bayesian MMRM on Change from Baseline Endpoints: E-RS: COPD total and subscale scores	StInt
2.10	2.5	PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC
2.11	2.6	PP		Type III Tests of Fixed Effects for Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC
2.12	2.7	PP		Analysis of Proportion of Responders According to Monthly Mean E-RS: COPD Scores up to Month 6	Responder Analysis Generalized linear model Endpoints: E-RS: COPD total and subscale scores	StInt, SAC
2.13	2.8	PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6: Interaction of Treatment with Other Factors	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Baseline E-RS: COPD Total Score (<10, >=10)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt
2.15	2.9	PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Smoking Status at Screening (Current, Former)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC
2.16		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Country	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt
2.17	2.10	PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by % Predicted FEV1 at Screening (<50, >=50)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC
2.18	2.11	PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Baseline CAT Score (<10, >=10)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt, SAC
2.19		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Exacerbation History (>=2 moderate/severe vs. 1 moderate/severe, prior year)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt
2.20		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by COPD Medication Grouping at Baseline (ICS+LABA+LAMA, ICS+LABA, LABA+LAMA, Other)	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by CMH Status at Baseline	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt
2.22		PP		Analysis of Change from Baseline Monthly Mean E-RS: COPD Total Score up to Month 6 by Season	Frequentist MMRM Endpoints: E-RS: COPD total score	StInt
	2.12			Summary of Responders to E-RS: COPD Total Score, SGRQ and CAT at Month 6	Include categories for E-RS, SGRQ, CAT, E-RS+SGRQ, E-RS+CAT. SGRQ+CAT, E-RS+SGRQ+CAT, None, Missing	Post SAC
Exacerbations						
2.23	2.13	PP		Summary of On-treatment HCRU Exacerbations		StInt, SAC
	2.14	PP		Summary of On-treatment Details of Moderate/Severe HCRU Exacerbations		SAC
	2.15	PP		Summary of On-treatment HCRU Exacerbations Treated with Antibiotics	Include row for how many subjects were receiving ICS for at least 7 days at the time of exacerbation	Post SAC
2.24	2.16	PP		Bayesian Analysis of On-treatment Moderate/Severe HCRU Exacerbations	Bayesian generalized linear model	StInt, SAC
2.25		ITT		Bayesian Analysis of On-treatment Moderate/Severe HCRU Exacerbations	Bayesian generalized linear model	StInt,
2.26	2.17	PP		Summary and Bayesian Analysis of Time to First On-treatment Moderate/Severe HCRU Exacerbation	Bayesian proportional hazards model	StInt, SAC

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27	2.18	PP		Summary and Bayesian Analysis of Time to First On-treatment Severe HCRU Exacerbation	Bayesian proportional hazards model	StInt, SAC
EXACT Events						
	2.19	PP		Summary of On-treatment EXACT Events		SAC
	2.20	PP		Bayesian Analysis of On-treatment EXACT Events	Bayesian generalized linear model	SAC
	2.21	PP		Summary and Bayesian Analysis of Time to First On-treatment EXACT Events	Bayesian proportional hazards model	SAC
SGRQ						
2.28	2.22	PP	PD4	Summary of Baseline SGRQ Scores	Include total column Total and domain scores	StInt, SAC
2.29	2.23	PP	PD4	Summary of SGRQ Scores	Include raw and change from baseline Total and domain scores	StInt, SAC
2.30	2.24	PP		Bayesian Analysis of Change from Baseline SGRQ Total Score up to Month 6	Bayesian MMRM on Change from Baseline Endpoints: SGRQ Total Score	StInt, SAC
2.31	2.25	PP		Analysis of Proportion of Responders According to SGRQ Total Scores up to Month 6	Responder Analysis Generalized linear model	StInt, SAC
CAT						
2.32	2.26	PP	PD4	Summary of Baseline CAT Score	Include total column	StInt, SAC
2.33	2.27	PP	PD4	Summary of CAT Score	Include raw and change from baseline	StInt, SAC

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34	2.28	PP		Bayesian Analysis of Change from Baseline CAT Score up to Month 6	Bayesian MMRM on Change from Baseline Endpoints: CAT Score	StInt, SAC
2.35	2.29	PP		Analysis of Proportion of Responders According to CAT Score up to Month 6	Responder Analysis Generalized linear model	StInt, SAC
2.36	2.30	PP		Analysis of Change from Baseline CAT Score up to Month 6: Interaction of Treatment with Other Factors	Frequentist MMRM Endpoints: CAT Score	StInt, SAC
2.37		PP		Analysis of Change from Baseline CAT Score up to Month 6 by Baseline E-RS: COPD Total Score (<10, >=10)	Frequentist MMRM Endpoints: CAT Score	StInt
2.38	2.31	PP		Analysis of Change from Baseline CAT Score up to Month 6 by Smoking Status at Screening (Current, Former)	Frequentist MMRM Endpoints: CAT Score	StInt, SAC
2.39		PP		Analysis of Change from Baseline CAT Score up to Month 6 by Country	Frequentist MMRM Endpoints: CAT Score	StInt
2.40	2.32	PP		Analysis of Change from Baseline CAT Score up to Month 6 by % Predicted FEV1 at Screening (<50, >=50)	Frequentist MMRM Endpoints: CAT Score	StInt, SAC
2.41	2.33	PP		Analysis of Change from CAT Score up to Month 6 by Baseline CAT Score (<10, >=10)	Frequentist MMRM Endpoints: CAT Score	StInt, SAC
2.42		PP		Analysis of Change from CAT Score up to Month 6 by Exacerbation History (>=2 moderate/severe vs. 1 moderate/severe, prior year)	Frequentist MMRM Endpoints: CAT Score	StInt

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.43		PP		Analysis of Change from Baseline CAT Score up to Month 6 by COPD Medication Grouping at Baseline (ICS+LABA+LAMA, ICS+LABA, LABA+LAMA, Other)	Frequentist MMRM Endpoints: CAT Score	StInt
2.44		PP		Analysis of Change from Baseline CAT Score up to Month 6 by CMH Status at Baseline	Frequentist MMRM Endpoints: CAT Score	StInt
2.45		PP		Analysis of Change from Baseline CAT Score up to Month 6 by Season	Frequentist MMRM Endpoints: CAT Score	StInt
Rescue Use						
2.46	2.34	PP	PD4	Summary of Baseline Mean Number of Puffs of Rescue Medication per Day using Diary Data	Include total column	StInt, SAC
2.47	2.35	PP	PD4	Summary of Monthly Mean Number of Puffs of Rescue Medication per Day using Diary Data up to Month 6	Include raw and change from baseline	StInt, SAC
2.48	2.36	PP		Analysis of Change from Baseline in Monthly Mean Number of Puffs of Rescue Medication per Day using Diary Data up to Month 6	MMRM on Change from Baseline	StInt, SAC
2.49	2.37	PP	PD4	Summary of Baseline Percentage Rescue-free Days using Diary Data	Include total column	StInt, SAC
2.50	2.38	PP	PD4	Summary of Percentage Rescue-free Days using Diary Data up to Month 6	Include raw and change from baseline	StInt, SAC
2.51	2.39	PP		Analysis of Change from Baseline in Percentage Rescue-free Days using Diary Data up to Month 6	MMRM on Change from Baseline	StInt, SAC

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	2.40	PP	PD4	Summary of Baseline Mean Number of Occasions of Rescue Medication per Day using Sensor Data	Include total column	SAC
	2.41	PP	PD4	Summary of Monthly Mean Number of Occasions of Rescue Medication per Day using Sensor Data up to Month 6	Include raw and change from baseline	SAC
	2.42	PP		Analysis of Change from Baseline Monthly Mean Number of Occasions of Rescue Medication per Day using Sensor Data up to Month 6	MMRM on Change from Baseline	SAC
	2.43	PP	PD4	Summary of Baseline Percentage Rescue-free Days using Sensor Data	Include total column	SAC
	2.44	PP	PD4	Summary of Percentage Rescue-free Days using Sensor Data up to Month 6	Include raw and change from baseline	SAC
	2.45	PP		Analysis of Change from Baseline Percentage Rescue-free Days using Sensor Data up to Month 6	MMRM on Change from Baseline	SAC
Physical Activity						
	2.46	PP	PD4	Summary of Baseline PROactive Score	Include total column Endpoints: PROactive Total Score and domain scores	SAC
	2.47	PP	PD4	Summary of PROactive Score up to Month 6	Include raw and change from baseline Endpoints: PROactive Total Score and domain scores	SAC

Efficacy: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.52		PP		Summary of Responses to C-PPAC Questionnaire at Each Visit		StInt
Subject Global Assessments						
	2.48	PP	PD4	Summary of Subject Global Assessments at Baseline	Include total column Endpoints: severity, activity limitation	SAC
	2.49	PP	PD4	Summary of Subject Global Assessments	Endpoints: severity, change in severity, activity limitation and change in activity limitation	SAC

14.11.6. Efficacy Figures

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
E-RS: COPD						
	2.1	PP		Daily Mean E-RS: COPD Scores over Time	Total and subscale scores Day -7 to Day 168	Post SAC
	2.2	PP		Daily Mean E-RS: COPD Scores over Time by Completion Status	Total and subscale scores Day -7 to Day 168 One page for completers and one page for subjects who withdrew	Post SAC
2.1	2.3	PP		Daily Mean Change from Baseline in E-RS: COPD Scores over Time	Total and subscale scores	StInt, SAC

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.2	2.4	PP		Daily Mean (± SE) Change from Baseline in E-RS: COPD over Time by Dose	Total and subscale scores; one panel for each DNX dose to include DNX and placebo data	StInt, SAC
2.3		Symptomatic		Daily Mean (± SE) Change from Baseline in E-RS: COPD over Time by Dose	Total and subscale scores; one panel for each DNX dose to include DNX and placebo data	StInt
	2.5	PP		Daily Mean (± SE) E-RS: COPD over Time by Dose	Total and subscale scores Day -7 to Day 168	Post SAC
2.4	2.6	PP		Bayesian Dose Response Model for E-RS: COPD Scores at Month 6	Total and subscale scores; overlaid with mean/CI from Bayesian longitudinal model	StInt, SAC
2.5		Symptomatic		Bayesian Dose Response Model for E-RS: COPD Total Score at Month 6	Total score; overlaid with mean/CI from Bayesian longitudinal model	StInt
2.6	2.7	PP		Posterior Mean (90% CrI) Change from Baseline in E-RS: COPD Scores over Time	Total and subscale scores	StInt, SAC
2.7		Symptomatic		Posterior Mean (90% CrI) Change from Baseline in E-RS: COPD Total Score over Time	Total score	StInt
2.8		ITT		Posterior Mean (90% CrI) Change from Baseline in E-RS: COPD Total Score over Time	Total score	StInt
2.9	2.8	PP		Adjusted Mean (90% CI) Change from Baseline in E-RS: COPD Total Score over Time	Total score	StInt, SAC
	2.9	PP		Adjusted Mean (90% CI) E-RS: COPD Total Score over Time	Total score	Post SAC

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS:COPD Total Score at Month 6 by Baseline E-RS: COPD Total Score (<10, >=10)	One panel for each factor on the same page	StInt
2.11	2.10	PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by Smoking Status at Screening (Current, Former)	One panel for each factor on the same page	StInt, SAC
2.12		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by Country	One panel for each factor, 4 panels per page	StInt
2.13	2.11	PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by % Predicted FEV1 at Screening (<50, >=50)	One panel for each factor on the same page	StInt, SAC
2.14	2.12	PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by Baseline CAT Score (<10, >=10)	One panel for each factor on the same page	StInt, SAC
2.15		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by Exacerbation History (>=2 moderate/severe vs. <2 moderate/severe, prior year)	One panel for each factor on the same page	StInt
2.16		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by COPD Medication Grouping at Baseline (ICS+LABA+LAMA, ICS+LABA, LABA+LAMA, Other)	One panel for each factor on the same page	StInt
2.17		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by CMH Status at Baseline	One panel for each factor on the same page	StInt

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18		PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score at Month 6 by Season	All factors on one plot	StInt
	2.13	PP		Empirical Distribution Function Plot of E-RS: COPD Total Scores at Baseline	Total and subscale scores	Post SAC
	2.14	PP		Empirical Distribution Function Plot of E-RS: COPD Total Scores at Month 6	Total and subscale scores	Post SAC
Exacerbations						
2.19	2.15	PP		Median Rate Ratio (90% CrI) of On-treatment Moderate/Severe HCRU Exacerbations		StInt, SAC
2.20		ITT		Median Rate Ratio (90% CrI) of On-treatment Moderate/Severe HCRU Exacerbations		StInt
2.21	2.16	PP		Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe HCRU Exacerbation		StInt, SAC
2.22	2.17	PP		Kaplan-Meier Plot of Time to First On-treatment Severe HCRU Exacerbation		StInt, SAC
EXACT Events						
	2.18	PP		Median Rate Ratio (90% CrI) of On-treatment EXACT Events		SAC
	2.19	PP		Kaplan-Meier Plot of Time to First On-treatment EXACT Event		SAC
SGRQ						
2.23	2.20	PP		Posterior Mean (90% CrI) Change from Baseline in SGRQ Total Score over Time		StInt, SAC
	2.21	PP		Mean (90% CI) SGRQ Total Score over Time	Baseline, Day 84 and 168	Post SAC

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
CAT						
2.24	2.22	PP		Posterior Mean (90% CrI) Change from Baseline in CAT Score over Time		StInt, SAC
	2.23	PP		Mean (90% CI) CAT Score over Time	Baseline, Day 84 and 168	Post SAC
2.25		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Baseline E-RS: COPD Total Score (<10, >=10)	One panel for each factor	StInt
2.26	2.24	PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Smoking Status at Screening (Current, Former)	One panel for each factor	StInt, SAC
2.27		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Country	One panel for each factor	StInt
2.28	2.25	PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by % Predicted FEV1 at Screening (<50, >=50)	One panel for each factor	StInt, SAC
2.29	2.26	PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Baseline CAT Score (<10, >=10)	One panel for each factor	StInt, SAC
2.30		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Exacerbation History (>=2 moderate/severe vs. 1 moderate/severe, prior year)	One panel for each factor	StInt

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.31		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by COPD Medication Grouping at Baseline (ICS+LABA+LAMA, ICS+LABA, LABA+LAMA, Other)	One panel for each factor	StInt
2.32		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by CMH Status at Baseline	One panel for each factor	StInt
2.33		PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score at Month 6 by Season	All factors on one plot	StInt
Rescue Use						
	2.27	PP		Daily Mean Number of Puffs of Rescue Medication per Day using Diary Data over Time	Day -7 to Day 168	Post SAC
2.34	2.28	PP		Least Squares Mean (90% CI) Change from Baseline in Mean Number of Puffs of Rescue Use per Day using Diary Data over Time		StInt, SAC
2.35	2.29	PP		Least Squares Mean (90% CI) Change from Baseline in Percentage of Rescue-free Days using Diary Data over Time		StInt, SAC
	2.30	PP		Daily Mean Number of Occasions of Rescue Medication per Day using Sensor Data over Time	Day -7 to Day 168	Post SAC
	2.31	PP		Least Squares Mean (90% CI) Change from Baseline in Mean Number of Occasions of Rescue Use per Day using Sensor Data over Time		SAC
	2.32	PP		Least Squares Mean (90% CI) Change from Baseline in Percentage of Rescue-free Days using Sensor Data over Time		SAC

Efficacy: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Conditional E-RS: COPD						
2.36-2.43	2.33-2.35	PP		Least Squares Mean (90% CI) Change from Baseline in E-RS: COPD Total Score over Time by *Factor*	Produced if an interaction between treatment and factor is significant at the 10% level Where *Factor* is defined in Section 7.3.1 One panel for each factor	StInt, SAC
Continue from above	Continue from above	PP		Least Squares Mean (90% CI) Change from Baseline in CAT Score over Time by *Factor*	Produced if an interaction between treatment and factor is significant at the 10% level Where *Factor* is defined in Section 7.3.1 One panel for each factor	StInt, SAC

14.11.7. Safety Tables

Safety: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)						
3.1	3.1	mITT	AE1	Summary of On-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	StInt, SAC
3.2	3.2	mITT	AE3	Summary of Common (>=5%) On-treatment Adverse Events by Overall Frequency	ICH E3	StInt, SAC

Safety: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3	3.3	mITT	AE1/AE3	Summary All On-treatment Drug-Related Adverse Events by [System Organ Class and] Preferred Term	ICH E3 Use AE1 for interim with text in [] in title Use AE3 for final reporting with text in [] omitted.	StInt, SAC
	3.4	mITT	AE15	Summary of Common (>=5%) Non-serious On-treatment Adverse Events by System Organ Class and Preferred Term (Number of Subject and Occurrences)	FDAAA, EudraCT	SAC
	3.5	mITT	AE1	Summary of Post-treatment Adverse Events		SAC
	3.6	ALLSUB	AE2	Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC
	3.7	mITT	AE5A	Summary of All On-treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3	SAC
	3.8	mITT	AE5A	Summary of On-treatment Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3	SAC
Serious and Other Significant Adverse Events						
	3.9	mITT	AE16	Summary of On-treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
	3.10	ALLSUB	AE1/AE3	Summary of Pre-treatment Serious Adverse Events by [System Organ Class and] Preferred Term		SAC
3.4	3.11	mITT	AE1/AE3	Summary of On-treatment Serious Adverse Events by [System Organ Class and] Preferred Term	Use AE1 for interim with text in [] in title Use AE3 for final reporting with text in [] omitted.	StInt, SAC

Safety: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5	3.12	mITT	AE1/AE3	Summary of On-treatment Fatal Serious Adverse Events by [System Organ Class and] Preferred Term	Use AE1 for interim with text in [] in title Use AE3 for final reporting with text in [] omitted.	StInt, SAC
3.6	3.13	mITT	AE1/AE3	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by [System Organ Class and] Preferred Term	IDSL Use AE1 for interim with text in [] in title Use AE3 for final reporting with text in [] omitted.	StInt, SAC
3.7	3.14	mITT		Summary of On-treatment Adverse Events of Special Interest		StInt, SAC
	3.15	mITT		Summary of On-treatment Pneumonia (AE and SAE) by ICS	AE and SAE Subjects who have an event in the 'Infective pneumonia' SMQ By subjects receiving ICS for at least 7 days at the time on pneumonia onset.	Post SAC
Laboratory: Chemistry						
3.8	3.16	mITT	LB1	Summary of Chemistry Changes from Baseline	ICH E3, include change from baseline of min/max value	StInt, SAC
3.9	3.17	mITT	LB17	Summary of Worst Case Chemistry Results by Potential Clinical Importance Criteria	ICH E3	StInt, SAC
Laboratory: Hematology						
3.10	3.18	mITT	LB1	Summary of Hematology Changes from Baseline	ICH E3, include change from baseline of min/max value	StInt, SAC
3.11	3.19	mITT	LB17	Summary of Worst Case Hematology by Potential Clinical Importance Criteria	ICH E3	StInt, SAC

Safety: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)						
3.12	3.20	mITT	LIVER1	Summary/Listing of Liver Monitoring/Stopping Event Reporting	IDSL – if there are very small number of events this summary will be replaced with a listing. Table title to be determined by content.	StInt, SAC
3.13	3.21	mITT	LIVER10	Summary/Listing of Hepatobiliary Laboratory Abnormalities	IDSL – if there are very small number of events this summary will be replaced with a listing. Table title to be determined by content.	StInt, SAC
ECG						
	3.22	mITT	EG1	Summary of ECG Findings	IDSL, include min/max value	SAC
	3.23	mITT	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL include change from baseline of min/max value	SAC
3.14	3.24	mITT	EG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	StInt, SAC
3.15	3.25	mITT	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	StInt, SAC
Vital Signs						
	3.26	mITT	VS1	Summary of Change from Baseline in Vital Signs	ICH E3, include change from baseline of min/max value	SAC
	3.27	mITT	VS7	Summary of Worst Case Vital Signs Results by Potential Clinical Importance Criteria	IDSL	SAC

Safety: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Spirometry						
3.16	3.28	mITT		Summary of Baseline Post-Bronchodilator FEV1 (L)	Post bronchodilator FEV1 Include total column	StInt, SAC
3.17	3.29	mITT		Summary of Post-Bronchodilator FEV1 (L)	Post bronchodilator FEV1 Include raw and change from baseline	StInt, SAC
3.18	3.30	mITT		Analysis of Change from Baseline Post-Bronchodilator FEV1 (L) up to Month 6	Frequentist MMRM Endpoints: Post bronchodilator FEV1	StInt, SAC
3.19	3.31	mITT		Type III Tests of Fixed Effects for Analysis of Change from Baseline Post-Bronchodilator FEV1 (L)	Frequentist MMRM Endpoints: Post bronchodilator FEV1	StInt, SAC
3.20	3.32	mITT		Summary of Baseline Post-Bronchodilator FVC (L)	Post bronchodilator FVC Include total column	StInt, SAC
3.21	3.33	mITT		Summary of Post-Bronchodilator FVC (L)	Post bronchodilator FVC Include raw and change from baseline	StInt, SAC
3.22	3.34	mITT		Analysis of Change from Baseline Post-Bronchodilator FVC (L) up to Month 6	Frequentist MMRM Endpoints: Post bronchodilator FVC	StInt, SAC
3.23	3.35	mITT		Type III Tests of Fixed Effects for Analysis of Change from Baseline Post-Bronchodilator FVC (L)	Frequentist MMRM Endpoints: Post bronchodilator FVC	StInt, SAC
	3.36	mITT		Summary of Baseline Post-Bronchodilator FEV1/FVC	Post bronchodilator FEV1/FVC Include total column	Post SAC
	3.37	mITT		Summary of Post-Bronchodilator FEV1/FVC	Post bronchodilator FEV1 Include raw and change from baseline Day 84 and 168	Post SAC

14.11.8. Safety Figures

Safety: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events						
	3.1	mITT	AE10	Plot of Common (>=5%) On-Treatment Adverse Events and Relative Risk	IDSL One page per active treatment compared to placebo Include AEs which have >=5% incidence in any treatment group	SAC
Laboratory						
3.1	3.2	mITT	LIVER14	Scatter Plot of Maximum Post-Baseline vs. Baseline for ALT	IDSL	StInt, SAC
3.2	3.3	mITT	LIVER9	Scatter Plot of Maximum Post-Baseline ALT vs. Maximum Post-Baseline Total Bilirubin	IDSL	StInt, SAC
3.3	3.4	mITT		Plot of Mean (95% CI) Neutrophil Counts over Time		StInt, SAC
	3.5	mITT		Plot of Mean (95% CI) Neutrophil Counts over Time for Subjects with Pneumonia		Post SAC
Spirometry						
	3.6	mITT		Mean (90% CI) Post-Bronchodilator FEV1 (L) over Time	Baseline, Day 84 and 168	Post SAC
3.4	3.7	mITT		Adjusted Mean (90% CI) Change from Baseline Post-Bronchodilator FEV1 (L) over Time		StInt, SAC
	3.8	mITT		Mean (90% CI) Post-Bronchodilator FVC (L) over Time	Baseline, Day 84 and 168	Post SAC
3.5	3.9	mITT		Adjusted Mean (90% CI) Change from Baseline Post-Bronchodilator FVC (L) over Time		StInt, SAC

Safety: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	3.10	mITT		Mean (90% CI) Post-Bronchodilator FEV1/FVC Ratio over Time	Baseline, Day 84 and 168	Post SAC
ECG						
3.6	3.11	mITT		Boxplot of Change from Baseline in QTcF by Time and Treatment		StInt, SAC

14.11.9. Pharmacokinetic Tables

SAC No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
4.1	PK	PKCT1	Summary of Danirixin Whole Blood Pharmacokinetic Concentration-Time Data (Dry Blood Spot)	Include geometric mean and 90% CI for the summary of blood concentration data	SAC
4.2	PK	PKPT4	Summary of Derived Danirixin Whole Blood Pharmacokinetic Parameters (Dry Blood Spot)		SAC
4.3	PK2	Table 3.10 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Concentration-Time Data Dry Blood Spot vs Wet Whole Blood Samples - Bland Altman Analysis		SAC
4.4	PK2	Table 3.12 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters Dry Blood Spot vs Wet Whole Blood Samples - Bland Altman Analysis		SAC
4.5	PK2	Table 3.11 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters Dry Blood Spot vs Wet Whole Blood Samples		SAC

SAC No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
4.6	PK2	Table 3.10 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Concentration-Time Data Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples - Bland Altman Analysis	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
4.7	PK2	Table 3.12 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples - Bland Altman Analysis	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
4.8	PK2	Table 3.11 Study 201037	Summary of Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC

14.11.10. Pharmacokinetic Figures

SAC No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
4.1	PK	PKCF1p	Individual Whole Blood Danirixin Concentration-Time Plots by Subject (Linear and Semi-log) (Dry Blood Spot)	1. X-axis displays actual relative time 2. Include line for LLQ along with footnote defining LLQ value 3. Include values below LLQ 4. Overlay Visit 3, 6, 7 and 10.	SAC
4.2	PK	PKCF6	Individual Whole Blood Danirixin Concentration-Time Plots by Day (Linear and Semi-log) (Dry Blood Spot)	1. X-axis displays actual relative time 2. Include line for LLQ along with footnote defining LLQ value 3. Include values below LLQ	SAC

SAC No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
4.3	PK	PKCF4	Mean (±SD) Whole Blood Danirixin Concentration-Time Plots (Linear and Semi-log) (Dry Blood Spot)	1. Include the full SD bars at each time point 2. X-axis displays planned relative time 3. Include line for LLQ along with footnote defining LLQ value 4. Overlay Visit 3, 6, 7 and 10.	SAC
4.4	PK	PKCF5	Median (Range) Whole Blood Danirixin Concentration-Time Plots (Linear and Semi-log) (Dry Blood Spot)	1. Include bars for range at each time point 2. X-axis displays planned relative time 3. Include like for LLQ along with footnote defining LLQ value 4. Overlay Visit 3, 6, 7 and 10.	SAC
4.5	PK	PK27	Median (Range) Pre-Dose Whole Blood Danirixin Concentration Versus Day (Linear and Semi-log) (Dry Blood Spot)	1. Include bars for range at each time point 2. X-axis displays Visit 3. Include like for LLQ along with footnote defining LLQ value 4. Visit include 3, 6, 7 and 10.	SAC
4.6	PK	Figure 11.206 Study 200163	Individual Whole Blood Pharmacokinetic Parameters (+Geometric Mean and 95% CI) versus Demographics	Demographics: Age, Weight, Gender. By day.	SAC
4.7	PK		Scatter Plot of Whole Blood Danirixin Concentration-by Day (Dry Blood Spot)		Post SAC
4.8	PK2	Figure 3.10 Study 201037	Individual Subject Danirixin Blood Concentration-Time Plot (Linear and Semi-Log) by Subject Dry Blood Spot vs Wet Whole Blood Samples		SAC

SAC No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
4.9	PK2	Figure 3.8 Study 2010137	Comparative Plot of Individual Subject Danirixin Blood Concentrations Dry Blood Spot vs Wet Whole Blood Samples		SAC
4.10	PK2	Figure 3.9 Study 201037	Bland-Altman Plot of Individual Subject Log-Transformed Danirixin Blood Concentrations Dry Blood Spot vs Wet Whole Blood Samples		SAC
4.11	PK2	Figure 3.10 Study 201037	Individual Subject Danirixin Blood Concentration-Time Plot (Linear and Semi-Log) by Subject Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
4.12	PK2	Figure 3.8 Study 2010137	Comparative Plot of Individual Subject Danirixin Blood Concentrations Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
4.13	PK2	Figure 3.9 Study 201037	Bland-Altman Plot of Individual Subject Log-Transformed Danirixin Blood Concentrations Sensitivity Analysis: Dry Blood Spot vs Wet Whole Blood Samples	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC

14.11.11. Pharmacokinetic / Pharmacodynamic Figure

Pharmacokinetic / Pharmacodynamic: Figures					
SAC No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1	PK		Scatter plot of PD endpoint versus Danirixin Concentration (Trough)	CAT Total Score Include Placebo imputed as DNX conc=0ng/mL, include DNX conc=NQ imputed as LLOQ/2, where LLOQ=5ng/mL By Day Different symbol for each treatment	Post SAC
5.2	PK		Scatter plot of Safety versus Danirixin Concentration (Trough)	Blood Neutrophil Count and C-reactive Protein (CRP) Highlight subjects with an on-treatment event in the 'Infective pneumonia' SMQ. Add footnote 'Note: Pneumonia may have occurred at any time during the study' Include Placebo imputed as DNX conc=0ng/mL, include DNX conc=NQ imputed as LLOQ/2, where LLOQ=5ng/mL By Day Different symbol for each treatment	Post SAC
5.3	PK		Quartile plot of Danirixin Concentration versus PD endpoint	CAT Total Score	Post SAC
5.4	PK		Quartile plot of Danirixin Concentration versus Safety endpoint	Blood Neutrophil Count and C-reactive Protein (CRP)	Post SAC

14.11.12. Biomarker Tables

Biomarker: Tables						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarkers						
6.1	6.1	mITT	LB1	Summary of C-reactive Protein (CRP) Changes from Baseline	ICH E3	StInt, SAC
6.2	6.2	mITT	LB1	Summary of Fibrinogen Changes from Baseline	ICH E3	StInt, SAC
	6.3	mITT		Summary of C-reactive Protein (CRP) for Subjects with Pneumonia	Screening, Baseline, Day 84 and 168 Subjects who have an event in the 'Infective pneumonia' SMQ	Post SAC
	6.4	mITT		Summary of Fibrinogen for Subjects with Pneumonia	Screening, Baseline, Day 84 and 168 Subjects who have an event in the 'Infective pneumonia' SMQ	Post SAC

14.11.13. Biomarker Figures

Biomarker: Figures						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarkers						
6.1	6.1	mITT		Boxplot of C-reactive Protein (CRP) by Time and Treatment	Screening, Baseline, Day 84 and 168	StInt, SAC
6.2	6.2	mITT		Boxplot of Fibrinogen by Time and Treatment	Screening, Baseline, Day 84 and 168	StInt, SAC
	6.2	mITT		Boxplot of C-reactive Protein (CRP) over Time for Subjects with Pneumonia	Screening, Baseline, Day 84 and 168 Subjects who have an event in the 'Infective pneumonia' SMQ	Post SAC
	6.4	mITT		Boxplot of Fibrinogen over Time for Subjects with Pneumonia	Screening, Baseline, Day 84 and 168 Subjects who have an event in the 'Infective pneumonia' SMQ	Post SAC

14.11.14. ICH Listings

ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition						
	1	ALLSUB	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
	2	mITT	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
	3	mITT	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
	4	mITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
	5	mITT	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations						
	6	mITT	DV2	Listing of Important Protocol Deviations	ICH E3 Listing also includes analysis population exclusions.	SAC
	7	ALLSUB	IE3	Listing of Screen Failure Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
	8	mITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC

ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Populations Analysed						
	9	mITT	SP3	Listing of Subjects Excluded from Any Population	ICH E3 ITT (Strategic interim only), mITT, PP, Symptomatic (Strategic interim only), PK and PK2 population	SAC
Demographic and Baseline Characteristics						
	10	mITT	DM2	Listing of Demographic Characteristics	ICH E3	SAC
	11	miTT	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications						
	12	mITT	CP_CM3	Listing of Non-COPD Concomitant Medications	IDSL	SAC
	13	mITT	CP_CM3	Listing of COPD Concomitant Medications		SAC
Exposure and Treatment Compliance						
	14	mITT	EX3	Listing of Exposure Data	ICH E3	SAC
EXACT Scores						
	15	mITT		Listing of E-RS: COPD Daily Scores	Total and subscale scores	SAC
Adverse Events						
1	16	mITT	AE8	Listing of All Adverse Events	ICH E3	StInt, SAC
	17	mITT	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
	18	mITT	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC

ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events						
	19	mITT	AE8 / AE8CPa	Listing of Fatal Serious Adverse Events	ICH E3	SAC
	20	mITT	AE8 / AE8CPa	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
	21	mITT	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
	22	mITT	AE8 / AECP8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
	23	mITT	AE8 / AECP8	Listing of Drug-Related Adverse Events	ICH E3	SAC
	24	mITT	AE8 / AECP8	Listing of Adverse Events of Special Interest	ICH E3	SAC
Hepatobiliary (Liver)						
	25	mITT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
	26	mITT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC
All Laboratory						
	27	mITT	LB5	Listing of Chemistry Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC
	28	mITT	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC
	29	mITT	LB5	Listing of Chemistry Values of Potential Clinical Importance		SAC

ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	30	mITT	LB5	Listing of Haematology Values of Potential Clinical Importance		SAC
	31	mITT	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
ECG						
	32	mITT	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
	33	mITT	EG3	Listing of ECG Values of Potential Clinical Importance		SAC
	34	mITT	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding		SAC
	35	mITT	EG5	Listing of Abnormal ECG Findings		SAC
Vital Signs						
	36	mITT	VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL	SAC

14.11.15. Non-ICH Listings

Non-ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition						
	37.	ALLSUB	ES9	Listing of Subjects Who Were Rescreened	Include Inclusion/ Exclusion/ Randomization Criteria Deviations	SAC
	38.	ALLSUB		Listing of Study Treatment Misallocations		SAC
Demographic and Baseline Characteristics						
	39.	mITT		Listing of Smoking History and Smoking Status		SAC
	40.	mITT		Listing of COPD History and Exacerbation History		SAC
	41.	mITT		Listing of Screening Spirometry Measures and GOLD Stages at Screening	Include % predicted category (</>=50%)	SAC
	42.	mITT		Listing of Baseline Symptomatic Characteristics	Contents as for table	SAC
Past and Current Medical History						
	43.	mITT		Listing of Medical Conditions		SAC
	44.	mITT		Listing of Family History of Cardiovascular Risk Factors		SAC
	45.	mITT		Listing of Percent Oxygen in Blood		SAC
Treatment Compliance						
	46.	mITT		Listing of Treatment Compliance		SAC

Non-ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
E-RS: COPD						
	47.	mITT		Listing of E-RS: COPD Baseline and Monthly Mean Scores	Include baseline and baseline category (</>=10) Total and subscale scores Include change from baseline and season	SAC
Exacerbations						
	48.	mITT		Listing of HCRU Exacerbation Data		SAC
EXACT Events						
	49.	mITT		Listing of EXACT Event Data		SAC
SGRQ						
	50.	mITT		Listing of SGRQ Scores	Total and domain scores Baseline, absolute and change from baseline	SAC
CAT						
	51.	mITT		Listing of CAT Scores	Total score Baseline, absolute and change from baseline and season	SAC
Rescue Use						
	52.	mITT		Listing of Derived Rescue Use from Diary	Monthly means Absolute, baseline and change from baseline	SAC

Non-ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	53.	mITT		Listing of Derived Rescue Use from Sensor	Monthly means Baseline, absolute and change from baseline	SAC
Physical Activity						
	54.	mITT		Listing of C-PPAC Questionnaire Responses		SAC
	55.	mITT		Listing of Activity Monitor Data		SAC
	56.	mITT		Listing of PROactive Scores	Total and domain scores Baseline, absolute and change from baseline	SAC
Subject Global Assessments						
	57.	mITT		Listing of Subject Global Assessments		SAC
Biomarkers						
	58.	mITT		Listing of Biomarkers		SAC
ECG						
2.	59.	mITT		Listing of Subjects with Maximum Post-Baseline QTcF increasing to over 500 msec or by 60 msec from Baseline		StInt, SAC
PK						
	60.	PK	PKCL1P	Listing of Danirixin Blood Concentration-Time Data – Dry Blood Spot Samples		SAC
	61.	PK	PKPL1P	Listing of Danirixin Blood Pharmacokinetic Parameter – Dry Blood Spot Samples		SAC
	62.	PK2	PKCL1P	Listing of Danirixin Blood Concentration-Time Data – Wet Whole Blood Samples		SAC

Non-ICH: Listings						
StInt No.	**SAC No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	63.	PK2	PKPL1P	Listing of Danirixin Blood Pharmacokinetic Parameter – Wet Whole Blood Samples		SAC
	64.	PK2	Listing 40 Study 201037	Supportive SAS Output from Statistical Analysis of Log-Transformed Danirixin Blood Pharmacokinetic Concentration Data - Bland Altman Analysis		SAC
	65.	PK2	Listing 42 Study 2101037	Supportive SAS Output from Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters - Bland Altman Analysis		SAC
	66.	PK2	Listing 41 Study 201037	Supportive SAS Output from Statistical Analysis of Log-Transformed Danirixin Pharmacokinetic Parameters		SAC
	67.	PK2	Listing 40 Study 201037	Supportive SAS Output from Statistical Analysis of Log-Transformed Sensitivity Analysis: Danirixin Blood Pharmacokinetic Concentration Data - Bland Altman Analysis	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
	68.	PK2	Listing 42 Study 2101037	Supportive SAS Output from Statistical Analysis of Log-Transformed Sensitivity Analysis: Danirixin Pharmacokinetic Parameters - Bland Altman Analysis	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC
	69.	PK2	Listing 41 Study 201037	Supportive SAS Output from Statistical Analysis of Log-Transformed Sensitivity Analysis: Danirixin Pharmacokinetic Parameters	excluding dry blood spot concentrations above the assay HLOQ of 1000 ng/mL	SAC

14.12. Appendix 12: Example Mock Shells for Data Displays

Mock shells will be created in a separate document.