Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan (RAP) for 201023: A Phase II, global, randomized study to evaluate the efficacy and safety of Danirixin (GSK1325756) co-administered with a standard-of-care antiviral (oseltamivir), in the treatment of adults hospitalized with influenza
Compound Number	:	GSK1325756
Effective Date	:	05-SEP-2017

Description :

1. The purpose of this RAP is to describe the planned analyses and output to be included in the Synoptic Report for study 201023. This document contains the RAP Amendment 01.
2. This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes all the planned analyses and outputs required for the end of study Synoptic Report for study 201023.
Protocol	• This RAP is based on the original protocol [(Dated: 12/Jul/2016) of study 201023(GSK Document No: 2016N281688_00] and eCRF Version 1
Primary Objective	• To assess the efficacy of treatment with IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to clinical response (TTCR)
Primary Endpoint	Time to Clinical Response (composite) • Hospital discharge **OR** • Normalization of: - Temperature; and - Oxygen status; and - Respiratory status/Heart Rate/SBP(normalization of 2 out of these 3 parameters)
Study Design	• Phase 2, randomized, double-blind (for IV DNX), placebo-controlled (for IV DNX) 3-arm study in adults to determine the efficacy and safety of IV DNX when coadministered (in all groups) with standard of care antiviral treatment (open-label oral 75 mg OSV) for patients hospitalized with influenza. • Enrolled Subjects will be randomized 2:2:1 to 15 mg FBE IV DNX, 50 mg FBE IV DNX, or matching placebo. All subjects will also receive open-label oral OSV, twice daily (given as standard of care). • Study treatment duration will be for up to 5 days. The investigator may elect to continue treatment with standard of care (OSV) after 5 days of study treatment. • The sample size of 300 was selected based on simulations to achieve at least 80% overall power under assumption of HR =1.5 for 50 mg of DNX FBE and HR =1.2 for 15 mg of DNX FBE and keep type I error less than 10% under no-effect assumption. The study was terminated early after 10 subjects were enrolled. • An Independent Data Monitoring Committee (IDMC) will perform monitoring and reviews of available safety and efficacy data. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to unblinding of the study data.
Planned Analyses	• The final analysis will occur when both accrual and follow-up are complete for all subjects.
Primary Analysis Populations	• 'Influenza Positive Population' (IPP) comprises of all subjects in the ITT-E population with influenza infection (positive influenza PCR or culture at any timepoint) confirmed by central lab testing.

Overview	Key Elements of the RAP
Hypothesis	• No formal hypotheses will be tested and only descriptive summaries will be created for the final analysis.
Primary Analyses	• Kaplan-Meier estimates for the median of TTCR for each treatment group and 95% confidence interval (CI) will be provided.
Secondary Analyses	• Median, and 95% CI for time to respiratory response will be provided. • Proportion of subjects with clinical response, and improved respiratory status will be summarized. • Frequency of antibiotic use • Frequency of adverse events (AEs) and serious adverse events (SAEs) • Frequency of adverse events of special interest (AESIs) • Change from baseline in clinical laboratory evaluations • Summarize standard pharmacokinetic parameters for IV DNX (i.e. AUC, Cmax, Cavg).
Exploratory Analyses	• Change in quantitative influenza viral load over time and change from baseline measured from nasopharyngeal swab samples as determined by qRT-PCR and quantitative virus culture (qVC) • Percentage of subjects with no detectable influenza viral RNA by qRT-PCR and qVC. • Percentage of subjects with co-infected viruses by multiplex RT PCR. • Percentage by type of co-infected viruses by multiplex RT PCR. • Quantitative and qualitative changes in exploratory biomarkers (may include but are not limited to: IL-8, procalcitonin, respiratory neutrophil cell counts, neutrophil elastase, and myeloperoxidase). • PK exposure for DNX and pharmacodynamic parameters. • FLU PRO questionnaire • Activities of daily living (Katz ADL Score)

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Given that the study has been terminated early and only 10 subjects have been enrolled, no formal hypothesis testing will be performed for the study. All analyses will be descriptive and not intended for making definitive conclusions. Only a selected set of originally planned analyses will be performed and all data will be listed.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• To assess the efficacy of treatment with IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to clinical response (TTCR)	Time to Clinical Response (composite) Hospital discharge **OR** Normalization of: - Temperature; and - Oxygen status; and - Respiratory status/Heart Rate/SBP(normalization of 2 out of these 3 parameters)
Secondary	
• To assess the efficacy of treatment with IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to respiratory response (TTRR)	Time to Respiratory Response defined as meeting at least one criterion below Return to pre-morbid oxygen requirement (subjects with chronic oxygen use), OR Return to no requirement of supplemental oxygen, OR Respiratory rate ≤24/min (without supplemental oxygen)
• To evaluate clinical measures of influenza illness following treatment with IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily	Time to absence of fever Time to improved oxygen status Time to improved heart rate Time to improved SBP Proportion of subjects with clinical response over time Proportion of subjects with improved respiratory status over time Time to improvement of ventilation status: modality, frequencies and durations of invasive and non-invasive ventilator support, duration of oxygen supplementation. Length of stay in the ICU Frequency of ICU admission and readmission Length of stay in the hospital Rates of development of septic shock Frequency of antibiotic use

Objectives	Endpoints
	Proportion of subjects with improvement in Ordinal scale of clinical efficacy over time : Death Mechanical vent In the ICU/ non MV Non-ICU hospitalization Hospital discharge
• To characterize the safety and tolerability of IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily	Frequency of adverse events (AEs) and serious adverse events (SAEs) Frequency of adverse events of special interest (AESIs) Change from baseline in clinical laboratory evaluations, and ECG parameters
• To characterize the pharmacokinetics of IV DNX in subjects hospitalized for influenza	Standard pharmacokinetic parameters for IV DNX (i.e. AUC, Cmax, Cavg).
Exploratory	
• To assess changes in influenza viral load from nasopharyngeal swabs following treatment with IV DNX twice daily given with oral oseltamivir compared to oral OSV twice daily; perform resistance analysis and a multiplex PCR assay with respiratory virus panel to assess coinfection.	Change in quantitative influenza viral load over time and change from baseline measured from nasopharyngeal swab samples as determined by qRT-PCR and quantitative virus culture (qVC) Percentage of subjects with no detectable influenza viral RNA by qRT-PCR and qVC. Percentage of subjects with co-infected viruses by multiplex RT PCR. Percentage by type of co-infected viruses by multiplex RT PCR. Change in quantitative viral load of other virus co-infections over time and change from baseline measured from nasopharyngeal swab samples, as determined by qRT-PCR. Frequency of emergent resistance to OSV
• To explore the effects of IV DNX twice daily given with oral oseltamivir compared to oral OSV twice daily with IV DNX placebo on biomarkers of inflammation and immune response from nasal samples or fluid, endotracheal samples, whole blood, bronchoalveolar lavage, and/or serum.	Quantitative and qualitative changes in exploratory biomarkers (may include but are not limited to: IL-8, procalcitonin, respiratory neutrophil cell counts, neutrophil elastase, and myeloperoxidase).
• To characterize the PK response	PK exposure for DNX and pharmacodynamic

Objectives	Endpoints
relationship of IV DNX.	parameters.
• To determine health outcome impact of IV DNX twice daily given with oral OSV compared to oral OSV twice daily	FLU PRO questionnaire Activities of daily living (Katz ADL Score) Activity level Hospital readmission rates

2.3. Study Design

Subjects meeting all eligibility criteria will be randomized 2:2:1 to one of three treatment groups in accordance with the central randomization schedule generated by Clinical Statistics prior to the start of the study, using validated internal software. All randomized subjects will take investigational drug or matching placebo twice daily for up to 5 days in the hospital.

2.4. Statistical Hypotheses

No statistical hypotheses will be formally tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

An Independent Data Monitoring Committee (IDMC) will perform monitoring and reviews of available safety and efficacy data. Details are specified in the IDMC charter. No formal interim analysis will be performed.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects enrol in the study at the time of study termination have completed the study, which is defined as completing the Day 45 assessment.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to Ramos NG procedures.

4. ANALYSIS POPULATIONS

Table 1 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Intent to Treat Exposed Population (ITT-E)	• Comprised of all randomized subjects who receive at least one dose of investigational product. Subjects will be assessed according to their randomized treatment, regardless of the treatment they receive.	• Study Population and disposition
Safety	• Comprised of all randomized subjects who receive at least one dose of IP. • This population will be based on the treatment the subject actually received.	• Safety
Influenza Positive Population (IPP)	• Comprised of all subjects in the ITT-E population with influenza infection (positive influenza PCR or culture at any timepoint) confirmed by central lab testing.	• Efficacy, Health Outcomes, Virology, Biomarker
PK	• Comprised of all subjects who underwent blood PK sampling during the study and from whom one or more blood concentration is determined.	• PK
All Subjects Screened	• Comprised of all subjects screened for inclusion in the study	• Study Population

NOTES :
Please refer to Appendix 13: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Treatment States and Phases
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance
11.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
11.10	Appendix 10: Multiple Comparisons & Multiplicity
11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
11.12	Appendix 12: Abbreviations and Trade Marks
Error! Reference source not found.	Appendix 13: List of Data Displays
11.14	Appendix 14: example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT-E population, unless otherwise specified.

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y[1]		
Reasons for Screen Failure			Y
Reasons for Study Withdrawal	Y[2]		Y
Reasons for Discontinuation of Study Treatment	Y		Y
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations			Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y [3]
Populations Analysed			
Study Populations	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y[1]		Y
Race and Racial Combinations	Y		Y[4]
Prior and Concomitant Medications			
Concomitant Medications			Y
Prior Exposure to Oseltamivir			Y
Exposure			
Exposure to Study Treatment	Y		Y
Other			
Flu Details (includes influenza subtypes)	Y[1]		Y
Past and Current Medical Conditions	Y		Y
Chronic underlying illness at baseline for Subjects with Renal Impairment			Y[5]
Ventilation and Oxygenation Status at Baseline and Any Time	Y		Y
Chest X-ray at Baseline			Y

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing

NOTES :

- Y = Yes display generated.

[1] For ITT-E and IPP
[2] Included in the Summary of Subject Disposition
[3] Listing also includes analysis population exclusions.
[4] Listing of race
[5] Renal impairment is based on Creatinine Clearance Criteria .

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

The primary efficacy analyses will be based on the IPP population, unless otherwise specified. Table 5 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

7.1.1. Overview of Planned Efficacy Analyses

Table 4 Overview of Planned Primary Efficacy Analyses

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
	Absolute						
Time to Clinical Response (TTCR)				Y[1]			Y
Proportion of Subjects Achieving Improved Clinical Response by End of Study				Y[1]			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data

[1]. Proportion of clinical response and Kaplan Meier estimates for the median of TTCR for each treatment group and 95% CI will be provided

7.1.2. Planned Efficacy Statistical Analyses

The clinical response is defined as hospital discharge due to clinical improvement or meeting following vital signs/ventilation criteria.

Sign of clinical response	**Response criteria**
Temperature[1]	≤36.6°C (≤97.9°F) – axilla/temporal, or ≤37.2°C (≤99°F) – oral, or ≤37.7°C (≤99.9°F) – rectal/core[5], tympanic
AND	
Oxygen saturation [2,3]	≥95% (without supplemental oxygen)
AND 2 out of the following 3 criteria:	
Respiratory status	• For subjects with chronic hypoxia and supplemental oxygen use: return to pre-morbid oxygen requirement, OR • For subject with supplemental oxygen use at study entry: need for supplemental oxygen (administered by any modality – ventilator, non-invasive ventilation, facemask, face-tent, nasal canula, etc) to no need for supplemental oxygen, OR • For subject without supplemental oxygen use and respiratory rate > 24/min at study entry: respiratory rate ≤24/min
Heart rate	≤100/min
Systolic blood pressure[4]	≥90 mmHg

1. Without the use of antipyretics within 8 hours
2. A subject with a history of chronic hypoxia (without supplemental oxygen) will satisfy normalization criteria for oxygen saturation if the value (without supplemental oxygen) is ≤2% from subject's historical oxygen saturation baseline as recorded within 12 months prior to enrolment as documented in the subject's medical records.
3. This requirement will be waived for subjects with a history of chronic supplemental oxygen requirement who have a baseline oxygen saturation <95% with supplemental oxygen, within 12 months prior to enrolment as documented in the subject's medical records.
4. Without inotropic support administered within 2 hours.
5. Core temperatures include rectal, indwelling catheters and Swan Ganz catheters.

Statistical Analyses
Endpoint(s)
• Time to Clinical Response (TTCR), days.
Derivation of TTCR
The clinical response based on vital signs/ventilation status requires 24-hour confirmation. Considering 2-hour assessment window, the response confirmation period is 22 hours, i.e. all assessments within 22 hours of the initial response and at least one at or beyond 22 hours need to meet the criteria in order for the response to be confirmed. Any missing scheduled assessment will be imputed with response value of 0 (1 means response). Only hospital discharge due to clinical response or a confirmed response based on vital signs/ventilation criteria is considered as event for the TTCR analysis. Hospital discharge due to clinical improvement can serve as 24-hour confirmation for the clinical response and the event date should be the onset of the vital signs response. Subjects who died prior to achieving a clinical response will be assigned a worst value of TTCR (99 days). All other subjects who did not achieve a confirmed response will be censored at the last assessment date of vital signs. For further details of the calculation of TTCR see Section 11.6.4.
Model Specification
Not applicable
Model Checking & Diagnostics
• Not applicable
Model Results Presentation
• Not applicable

Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses or subgroup analyses will be performed given the small number of subjects.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the IPP population, unless otherwise specified. Table 5 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays. Given the small number of subjects, only time to respiratory response will be summarized. Data relevant to other secondary endpoints will be listed including vital signs, ventilation status, hospital discharge, hospital re-admission, and ICU stay.

Table 5 Overview of Planned Secondary Efficacy Analyses

Endpoint	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
	Absolute						
Time to Respiratory Response (TTRR)				Y[1]			

[1] Proportion of clinical response and Kaplan Meier estimates for the median of TTCR for each treatment group and the median difference and 95% CI between two comparisons: each DNX arm and OSV will be provided

8.2. Safety Analyses

8.2.1. Overview of Planned Adverse Events Analyses

The safety analyses will be based on the Safety population, unless otherwise specified. The summaries include on-treatment and post-treatment assessments unless otherwise noted.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 6 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and Maximum Grade	Y		Y
All AEs by Overall Frequency	Y		
Grade 2-4 AEs by Overall Frequency	Y		
All Drug-Related AEs by Overall Frequency	Y		
All Non-Serious AEs by Overall Frequency	Y		
Drug-Related Grade 2-4 AEs by Overall Frequency	Y		
Relationship Between AE SOCs, PT & Verbatim Text			Y
Listing of Adverse Events for Subjects with Neutropenia by Grade (>=Grade 1)	Y[1]		
Serious and Other Significant AEs			
Fatal Serious AEs			Y
Non-Fatal Serious AEs	Y		Y
Serious AEs by SOC	Y		
Reasons for Considering as a Serious AE			Y
Drug-Related Non-Fatal Serious AEs	Y		
Drug-Related Serious AEs by SOC	Y		
Adverse Events Leading to Withdrawal from Study by Overall Frequency			Y
Adverse Events Leading to Permanent Discontinuation of Study Treatment by Overall Frequency			Y
Summary of Serious Adverse Events by System Organ Class and Preferred	Y		

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Term (Number of Subjects and Occurrences)			
Summary of Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Y		

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1].Toxicity Grading is based on the Division of AIDS Grading (Section 12.5 of the protocol)

8.2.2. Overview of Planned Clinical Laboratory Analyses

The safety analyses will be based on the Safety population, unless otherwise specified. The summaries include on-treatment and post-treatment assessments unless otherwise noted.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Summary of Data Supporting Safety Halting Criteria	Y[1]					
Chemistry Changes from Baseline				Y		
Creatinine by Visit	Y	Y		Y		
Hematology Changes from Baseline				Y		
Individual Plot of Absolute Neutrophils Count by Visit by Subject		Y				
All Laboratory						
Summary of Maximum Treatment Emergent Toxicities of All Lab Parameters	Y					
Laboratory Data Abnormalities of Potential Clinical Importance (Grade 3-4)						Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data

[1] Summary includes the proportion of subjects with creatinine increase of 0.5 mg/dl on 2 consecutive visits

8.2.3. Overview of Planned Other Safety Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
All ECG Values for Subjects with a Value of PCI[1]			Y			
Abnormal ECG Findings[2]			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] When QTc data is evaluated for PCI, all of the QTcB, QTcF and QTc collected in the eCFR are considered. Any one of the three meeting the PCI range is identified as an ECG event of PCI..
[2] When QTc data is evaluated for ECG abnormality, all of the QTcB, QTcF and QTc collected in the eCFR are considered. Any one of the three meeting the abnormality criteria is identified as an abnormal ECG Finding.

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

PK samples will be drawn on Day 1 (pre-dose, prior to 2nd dose), Days 3 and 5 to coincide with PD measurements (biomarkers) and additionally drawn on Day 3 (5th or 6th dose) at 0.5, 1 (end of infusion), 1.5, 2, 3, 4, 8 and 12 hours post-dose.

Table 9 provides an overview of the planned analyses with full details being presented in Appendix 13: List of Data Displays.

Table 9 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
DNX Concentrations	Y	Y		Y	Y	Y		
DNX PK Parameters		Y		Y		Y		

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.3.2. Drug Concentration Measures

Concentrations of Danirixin (GSK1325756) in blood will be listed and summarised by treatment group, day and nominal time.

Individual blood concentration-time profiles and median/mean profiles by treatment group will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot).

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 11.5.3 Reporting Process & Standards).

8.3.3. Pharmacokinetic Parameters

8.3.3.1. Deriving Pharmacokinetic Parameters

Pharmacokinetic parameters described in Table 10 will be determined from the concentration-time data, as data permits.

Table 10 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-12)	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

Parameter	Parameter Description
	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.
Cavg	Average concentration.

8.3.3.2. Statistical Analysis of Pharmacokinetic Parameters

No formal statistical analysis of derived pharmacokinetics parameter will be performed.

8.3.4. Population Pharmacokinetic (PopPK) Analyses

Given the small number of subjects enrolled population PK analysis for this study will not be performed.

8.4. Biomarker Analyses

8.4.1. Overview of Planned Biomarker Analyses

The Biomarker analyses will be based on the Influenza Positive Population, unless otherwise specified.

Table 11 provides an overview of the planned Biomarker analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 11 Overview of Planned Biomarker Analyses

[Endpoint / Parameter/ Display Type]	Untransformed							
	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Serum Biomarkers			Y	Y				
Nasal wash biomarkers[1]			Y	Y				
Nasal SAM strips biomarkers			Y	Y				
BAL Biomarker			Y	Y				

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] includes neutrophil count

8.5. Pharmacodynamic / Biomarker Statistical Analyses

8.5.1. Overview of Planned Pharmacodynamic / Biomarker Analyses

The Pharmacodynamic / Biomarker analyses will be based on the Influenza Positive Population, unless otherwise specified.

Table 12 provides an overview of the planned Biomarker / Pharmacodynamic analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 12 Overview of Planned Pharmacodynamic / Biomarker Analyses

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Biomarkers vs. Biomarkers			Y[1]					
Area under the curve for Serum Biomarkers TTCR			Y[2]					
Area under the curve for Nasal wash biomarkers – TTCR			Y[2]					
Area under the curve for Nasal SAM Strips biomarkers – TTCR			Y[2]					
Area under the curve for BAL biomarkers – TTCR			Y[2]					
Area under the curve for Serum Biomarkers – TTRR			Y[2]					
Area under the curve for Nasal wash biomarkers – TTRR			Y[2]					
Area under the curve for Nasal SAM biomarkers – TTRR			Y[2]					
Area under the curve for BAL biomarkers – TTRR			Y[2]					

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Matrix comparative plot of individual scatter plot of biomarkers vs. biomarkers for Each Biomarker. The x and the y-axis will include Serum, Nasal Wash, Nasal SAM Strips and BAL. Include the Pearson's correlation coefficient and p-value.

[2] Individual scatter plot of area under the curve biomarkers vs Time to Clinical Response, Time to Respiratory Response.

8.6. Pharmacokinetic / Pharmacodynamic Analyses

Relationships between Danirixin systemic exposure and the following pharmacodynamic measures will be explored graphically:

- Target engagement biomarker: IL-8, respiratory neutrophil cell counts, neutrophil elastase, and myeloperoxidase.

Pharmacokinetic/pharmacodynamic modelling may be attempted to describe any relationship including appropriate models for longitudinal variables versus systemic exposure. Results of PK/PD modelling analysis will be done under a separate Reporting and Analysis Plan and will be reported separately from the main CSR.

8.7. Health Outcome Analyses

8.7.1. Overview of Planned Health Outcome Analyses

The health outcome analyses will be based on the IPP population, unless otherwise specified.

Table 13 Overview of Planned Health Outcome Analyses

Endpoints	Absolute				Change from BL			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
KATZ ADL				Y		Y		
Flu PRO		Y		Y		Y		

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9. VIROLOGY ANALYSES

9.1. Overview of Planned Virology Analyses

The virology analyses will be based on the IPP population, unless otherwise specified.

Table 14 provides an overview of the planned analyses, with full details being presented in Appendix 13: List of Data Displays.

Table 14 Overview of Planned Virology Analyses

Endpoints	Absolute				Change from BL			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Influenza Viral Load by qRT-PCR				Y		Y[2,3]	Y[1,2,3]	
Influenza Viral Load by qVC				Y		Y[2,4]	Y[1,2,4]	

Endpoints	Absolute				Change from BL			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Resistance Associated Mutations Detected in the NA Gene by Subtype - - Nasopharyngeal		Y		Y				
Resistance Associated Mutations Detected in the HA Gene by Subtype - - Nasopharyngeal		Y		Y				
Proportion of Subjects - Positive Other Viruses by Multiplex		Y						

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Change from baseline plot for nasopharyngeal
[2] For nasopharyngeal
[3] Overall virus and by subtype
[4] For subjects culture positive at baseline, if warranted.

9.2. Planned Virology Statistical Analyses

qVC data will be summarized for subjects who are culture positive at baseline. For the RT-PCR summaries for Flu A and Flu B combined, coinfected subjects values will be averaged.

The following is a list of viruses detected in the multiplex assay:

- Adenovirus
- Coronavirus 229E
- Coronavirus HKU1
- Coronavirus OC43
- Coronavirus NL63
- Human Metapneumovirus
- Human Rhinovirus/Enterovirus
- Influenza A
- Influenza A/H1
- Influenza A/H1-2009
- Influenza A/H3
- Influenza B
- Parainfluenza 1

- Parainfluenza 2
- Parainfluenza 3
- Parainfluenza 4
- RSV A+B

For the viruses with multiple subtypes, the data will be summarized by same virus family (e.g. corona virus, parainfluenza, and RSV, influenza A)

The list of mutations which includes but is not limited to H275Y will be provided only if the data is available.

10. REFERENCES

FDA. *Guidance for Industry.* Center for Drug Evaluation and Research, United States Food and Drug Administration; 1999. Population Pharmackinetics.

11. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Time and Events
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Section 11.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.8	Appendix 8: Values of Potential Clinical Importance
Section 11.9	Appendix 9: Examination of Covariates and Subgroups
Section 11.10	Appendix 10: Multiple Comparisons and Multiplicity
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Other RAP Appendices	
Section 11.12	Appendix 12: Abbreviations & Trade Marks
Section 11.13	Appendix 13: List of Data Displays
Section 11.14	Appendix 14: Example Mock Shells for Data Displays

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

No Per Protocol Population will be used in the analysis.

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

Table 15 Time and Events Table: Assessments at Baseline and During Treatment

	Eligibility Assessments	During Treatment - 5 days[a] Inpatient						Post-treatment (PT) Inpatient
Procedures		**Baseline/ Study Day 1[a]**	**Study Day 2**	**Study Day 3**	**Study Day 4**	**Study Day 5 /day of last dose[a]**	**Study Day 6 if applicable[b]**	
Written informed consent	X	X						
Subject demography	X	X						
Physical examination[c]		X	X	X	X	X	X	Daily
Influenza Test – locally performed (equipment provided by GSK)	X	X						
Medical/Prior Medication/Drug/Smoking History	X	X						
HIV and Liver Disease History[d]	X	X						
Influenza symptoms[e]	X	X						
HIV, Hep B and Hep C Test[f]	X	X						
Chronic underlying illness assessment	X	X						
Inclusion/Exclusion Criteria	X							
Safety/Efficacy Assessments								
Chest X-ray[g]		X						
ECG[h]	X	X				X	X	
Adverse events		X	X	X	X	X	X	Daily
Concomitant medications[i]		X	X	X	X	X	X	Daily
Complications of influenza/associated antibiotic use[j]		X	X	X	X	X	X	Daily
Vital signs (temperature, HR, BP, respiratory rate, oxygen saturation, ventilation status)[k]	X	X	X	X	X	X	X	3 x Daily

	Eligibility Assessments	During Treatment - 5 days[a] Inpatient						Post-treatment (PT) Inpatient
Procedures		**Baseline/ Study Day 1[a]**	**Study Day 2**	**Study Day 3**	**Study Day 4**	**Study Day 5 /day of last dose[a]**	**Study Day 6 if applicable[b]**	
Flu PRO		X	X	X	X	X	X	Daily
Katz Activities of Daily Living[l]		X	X	X	X	X	X	Daily
Activity level[m]		X	X	X	X	X	X	Daily
Laboratory Assessments								
Chemistry including Liver Function Tests (Local+Central)[n]	X	X		X		X	X	Day 6,7,8
Serum creatinine (Local+Central) [o]	X	X	X	X	X	X	X	Day 6,7,8
Hematology (Local+Central) [p]	X	X		X		X	X	Day 6,7,8
Urine Output [q]		X	X	X	X	X	X	
Pregnancy test[r]	X	X						PT Day 3
Nasopharyngeal swab[s]		X		X		X	X	Day 8,12,16, 20,24,28 ,32
Nasal Swab[t]	X	X						
BAL[u]		X		X		X	X	
Endotracheal aspirate[v]		X		X		X	X	Day 8,16,24, 32, 45
Nasal SAM strips (biomarkers)[w]		X		X		X	X	Day 8,16,24, 32, discharge or Day 45
Nasal washes[x]		X		X		X	X	Day 8,16,24, 32, discharge or Day 45
Exploratory Biomarkers (Blood Sample)		X		X		X	X	Day 8,16,24, 32, discharge or Day 45
PK sample (Dried Blood Spot)[y]		X		X		X	X	
Genetics Sample (Blood Sample)[z]		X						
Transcriptomics (Blood Sample)[z]		X		X		X	X	Day 8, 16, 24,

	Eligibility Assessments	During Treatment - 5 days[a] Inpatient						Post-treatment (PT) Inpatient
Procedures		**Baseline/ Study Day 1[a]**	**Study Day 2**	**Study Day 3**	**Study Day 4**	**Study Day 5 /day of last dose[a]**	**Study Day 6 if applicable[b]**	
								32, discharge or Day 45
Study Treatments								
Administration of investigational medication (IV) and oseltamivir (oral) twice daily		**X**	**X**	**X**	**X**	**X**	**X**	

a. A 'Day' is defined as a 24 hour period (Treatment Day), therefore depending on the start time of the first dose of IV DNX, a Treatment Day may span two calendar days.
b. Day 6 assessments only applicable if last day of dose of randomized treatment is on Day 6 (i.e for subjects who received first dose after 12 noon on Baseline/Day 1.
c. Physical exam to be performed twice daily for subjects in the sentine cohort.
d. Enrollment into the study will be based on history of diagnosis of HIV and liver disease. Blood samples will be analyzed after enrollment to retrospectively determine if subject is HIV, Hep B or Hep C postivie; however, results will not be available until after completion of dosing.
e. Influenza symptoms to be assessed only at baseline for inclusion.
f. Enrollment into the study will be based on any history of diagnosis of HIV and liver disease.
g. Chest X-ray at Baseline and whenever clinically indicated.
h. ECG: For the ECG on Baseline/Day 1, one 12-lead ECG (can be done within approximately 24 hours prior to dosing). At Baseline and on Day 5 or last treatment day, a monitoring strip can be utilized if a 12-lead ECG cannot be performed.
i. Concomitant medications for influenza treatment of the current episode to be recorded from Day -7 (i.e. one week prior to baseline), if available.
j. Complications of influenza such as bacterial pneumonia, pneumothorax, pleural effusion, ARDS, myositis, encephalitis, myocarditis, and associated antibiotic use will be recorded on all assessment days.
k. Vital signs and ventilation status to be assessed three times daily during the treatment period between approximately 8 AM and 8 PM.
l. Katz ADL score collected once daily while hospitalized.
m. Activity level to be recorded as one of three responses (bed rest, limited ambulation or unrestricted) everyday while hospitalized
n. Chemistry panel including Liver Function Tests to be required once every other day during treatment (local testing (L) of LFTs for subject management as well as central laboratory testing (C)).
o. Serum creatinine level required at Baseline and twice daily during treatment for subjects in the sentinel cohort. For all other subjects, serum creatinine level required at Baseline and once daily during treatment (local testing (L) for subject management as well as central testing(C)).
p. Hematology panel including CBC with differential required every other day during treatment (local testing (L) for subject management as well as central testing(C))
q. Urine output to be measured twice daily for subjects in the sentinel cohort.
r. Ultrasensitive urine or blood pregnancy test required in women of childbearing potential prior to dosing and 3 days post last dose of study treatment.
s. Nasopharyngeal swab will be used for influenza Subtype RT-PCR, qRT-PCR, quantitative culture and may also be used for rapid influenza diagnosis; Will also be used for viral genotyping and phenotyping if needed and multiplex PCR assay.
t. Nasal swab collected for influenza diagnostic test or other local test for influenza diagnosis

u. BAL samples (for biomarkers) are requested only if the procedure/sampling is being carried out for routine management of the patient and at any timepoint throughout the study
v. Endotracheal aspirates (biomarkers/neutrophil counts) are required for subjects who are intubated.
w. Nasal samples for biomarkers will be collected at the days indicated from all subjects using nasal SAM strips.
x. An optional procedure, nasal wash, will be used to collect nasal samples from as many non-intubated subjects as feasible.
y. PK samples will be drawn on Day 1 (pre-dose), Days 3 and 5 to coincide with PD measurements (nasal washes if done, endotracheal samples and a blood draw for exploratory biomarkers). In sentinel cohort 1 (less severe subjeccts with normal renal function), PK samples will be additionally drawn on Day 3 at pre-dose, and 0.5, 1 (end of infusion), 1.5, 2, 3, 4, 8 and 12 hours post-dose. **Note: PK draws must be collected from the opposite arm from the infusion arm.**
z. Informed consent for optional substudies (e.g., genetic research and transcriptomics), must be obtained before collecting samples. In subjects who consent, a blood sample for genetic research is collected at the baseline visit, or at the earliest point possible during the treatment period for genetic research testing; blood samples for transcriptomics are taken on each of the indicated days and used to evaluate changes in transcriptome profiles.

Table 16 Time and Events Table: Post-Treatment and Post-Discharge Assessments

	Post-Discharge Visits/TCs and Assessments Outpatient [a]					
Procedures	**PT Day 3 (Visit)**	**Study Day 8 (TC)**	**Study Day 15 (TC)**	**Study Day 22 (TC)**	**Study Day 30 (TC)**	**Study Day 45 (Visit)**
Safety/Efficacy Assessments						
Adverse events	**X**	X	**X**	**X**	**X**	**X**
Concomitant medications	**X**	X	**X**	**X**	**X**	**X**
Brief Physical Exam	**X**					X
Complications of influenza / associated antibiotic use[b]	**X**	X	**X**	**X**	**X**	**X**
Temperature	**X**	X	**X**	**X**	**X**	**X**
Other Vital signs (HR, BP, respiratory rate, oxygen saturation, ventilation status)[c]	**X**					**X**
Flu PRO[d]	**Daily through Day 14**	**Daily through Day 14**	**X**	**X**	**X**	**X**
Katz Activities of Daily Living[e]	**X**	**X**	**X**	**X**	**X**	**X**
Activity level[f]	**Daily through Day 14**	**Daily through Day 14**	**X**	**X**	**X**	**X**
Laboratory Assessments						
Clinical chemistryincluding LFTs[g] (Local+Central)	**X**					X
Serum Creatinine[h] (Local+Central)	**X**					X
Hematology[i] (Local+Central)	**X**					X
Pregnancy test[j]	**X**					
Nasopharyngeal swabs	**X**					
Exploratory Biomarkers (Blood Sample)[k]	**X**					X
Transcriptomics (blood	**X**					X

sample)[l]						
Nasal SAM strips (biomarkers)[m]	**X**					X
Nasal washes[m]	**X**					X
Hospital Readmission Status	X	X	X	**X**	**X**	**X**

a. Following discharge from hospital, outpatient clinic visit/TC schedule of assessments will be followed for those patients who are discharged before Day 45. For 5 days treatment, PT Day 3 will be the same as Day 8 and will be a clinic visit.
b. Complications of influenza such as bacterial pneumonia, pneumothorax, pleural effusion, ARDS, myositis, encephalitis, myocarditis, and associated antibiotic use will be recorded on all assessment days.
c. Vital signs and ventilation status will be assessed at clinic visits (PT Day 3 and Day 45).
d. FLU PRO to be measured once daily through Study Day 14.
e. Activities of Daily Living (Katz Scale) to be done at clinic visits and at TCs.
f. Activity level assessed by reporting on a 3 point scale of bed rest (1), limited ambulation (2) or unrestricted (3) to be done daily through Study Day 14.
g. Clinical chemistry including LFTs to be required once every other day until PT Day 3 (for LFTs, local testing for subject management until PT Day 3; central testing for all assessments, including at Day 45).
h. Serum creatinine required once every day until PT Day 3 (local testing for subject management until PT Day 3; central testing for all assessments, including at Day 45).
i. Hematology panel including CBC with differential required once every other day until PT Day 3 (local testing for subject management until PT Day 3; central testing for all assessments, including at Day 45).
j. Ultrasensitive urine pregnancy test required in women of childbearing potential on PT Day 3.
k. Blood samples will be collected for exploratory biomarkers at PT Day 3, and at Study Day 45.
l. Blood samples for transcriptomics will be collected on PT Day 3 and Study Day 45 and are optional. Samples will be collected only from those subjects who provide informed consent for genetic research.
m. Nasal samples for biomarkers will be collected at PT Day 3 and Study Day 45 from all subjects using nasal SAM strips. In addition, an optional procedure, nasal wash, will be used to collect nasal samples from as many non-intubated subjects as feasible.

11.3. Appendix 3: Assessment Windows

This study will not use assessment windows.

11.4. Appendix 4: Treatment States and Phases

11.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified.

Treatment Phase	Definition
Pre-Treatment	Date< Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

11.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

11.4.2.1. Treatment States for Concomitant Medications Data

Treatment State	Definition
Pre- Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post Treatment	Date > Study Treatment Stop Date

NOTES:

- If the study treatment stop date is missing then the assessment will be considered to be On-Treatment. "On-Study" is considered assessment on-treatment and post-treatment.

11.4.2.2. Treatment States for AE Data

Unless otherwise noted, AE summaries will include both On-Treatment and Post-Treatment AEs.

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ Lag Time]
Post-Treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Drug-related	If relationship is marked 'YES' on InForm OR value is missing

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	15 mg FBE IV DNX BID +75 mg OSV BID	15 mg DNX +OSV	2
B	50 mg FBE IV DNX BID + 75 mg OSV BID	50 mg DNX +OSV	3
C	IV DNX placebo BID + 75 mg OSV BID	PBO + OSV	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

11.5.2. Baseline Definition & Derivations

11.5.2.1. Baseline Definitions

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1	
Vital Signs (temperature, HR, BP, respiratory rate, oxygen status, ventilation status)	X	X	Day 1
12 Lead ECG	X	X	Day 1
Laboratory parameters	X	X	Day 1
Nasopharyngeal Swab		X	Day 1
Nasal Swab	X	X	Day 1
Nasal SAM strips (biomarkers)		X	Day 1
Nasal wash biomarker		X	Day 1
BAL biomarkers		X	Day 1
Serum Biomarkers		X	Day 1
Katz ADL		X	Day 1
Flu PRO		X	Day 1

For all endpoints (unless stated otherwise) the baseline value will be the latest pre-dose assessment. This is generally expected to be from the Day 1 visit, although such values may be missing or unscheduled assessments may be performed before treatment start.

11.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

11.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS and TSCG software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Area	: \ARPROD\GSK1325756\MID201023\Final_xx
QC Spreadsheet	: \ARWORK\GSK1325756\MID201023\Final_xx\documents
Analysis Datasets	

Reporting Process
• Final analysis and IDMC datasets will be created based on Integrated Data Standards Library (IDSL). • RTF files will be generated for final analysis.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • 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.	
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. • 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 subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures, unless otherwise stated. • Unscheduled visits will be included in the maximum toxicity or maximum change from baseline for toxicity tables. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD)

Reporting Standards	
Summary Statistics (Log Transformed)	of logged data and between geometric coefficient of variation (CVb (%)) will be reported. ○ CV_b (%) = √ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One 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. • If there are two values within a visit the value closest to the planned/target day for that visit will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Treatment Start Date
Treatment start date is defined as follows: • Treatment start date is the date entered onto the IP exposure CRF for when study treatment started.
Study Day

• Calculated as the number of days from initial study treatment start date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment Start Date → Study Day = Ref Date –Treatment Start Date
  • Ref Data ≥ Treatment Start Date → Study Day = Ref Date – (Treatment Start Date) + 1
 	
Note that Treatment Start Date is considered to be on Study Day 1 and the day before this is Study Day -1; i.e., there is no Study Day 0.

Post-baseline
• Post-baseline refers to the combined time periods of On-treatment and Post-treatment.

11.6.2. Study Population

Demographics
Age
• Age, in whole years, will be calculated with respect to the subject's Screening visit. • GSK standard IDSL algorithms will be used for calculating age where birth date. • Birth date will be presented in listings as 'YYYY'.

Demographics
• Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.
Body Mass Index (BMI)
• If not already provided, BMI will be calculated as **Weight (kg) / [Height (m)]^2**
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

11.6.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
• Machine-read values of RR, QTcB or QTcF should not be replaced with re-derived values • When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$
Laboratory Parameters
• Influenza Virus load data from Viroclinics will be imputed as following: • LLOQ and LLOD per subtype are dependent on the data, assume the values are **x.xx, y.yy, z.zz, and w.ww** for LLOQ, LLOD for qPCR A and q PCR B, respectively

ECG Parameters

- qPCR A: LLOQ=: x.xx log vp/ml, LLOD: y.yy log vp/ml
  - When CT neg (i.e. qPCRA<LLOD), impute y.yy - 0.01
  - When qPCRA between LLOD and LLOQ, impute x.xx – 0.01
  - When qualitative results are derived from qPCR: when CT is positive value then "Virus detected" and when CT is neg then "Virus not detected".
- qPCR B: LLOQ: z.zz log vp/ml, LLOD:w.ww log vp/ml
  - When CT neg (i.e. qPCRB <LLOD), impute w.ww – 0.01.
  - When qPCRB between LLOD and LLOQ, impute z.zz – 0.01
  - When qualitative results are derived from qPCR: when CT is positive value then "Virus detected" and when CT is neg then "Virus not detected".
- TCID50: LLOQ = 0.75
  - When <0.75 impute 0.75 – 0.01 = 0.74.
  - When qualitative results are derived from TCID50: when TCID50 <0.75 impute "No Virus Isolated", when >0.75 impute "Virus Isolated".

- For other laboratory values, if laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. If a character value starting with "<=x", then the numeric value will be x.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' or '>=x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

11.6.4. Efficacy

Time to Clinical Response (TTCR)

TTCR will be derived as detailed in Section 7.1.2 The following is further considerations for the derivation of TTCR

- If an assessment time is missing the following times will be used in the calculation of TTCR: 8:00, 14:00, 20:00 respectively for morning, afternoon and evening assessments. The imputation will not be done for the study day 1.
- If the subject was discharged but is missing the date of discharge then the latest day from individual components will be used. If subject was discharged but the time of discharge is missing, 12:00 time will be used.
- If the subject withdraws consent on the same day as hospital discharge, TTCR will not be considered a failure.

- Deaths which occur after clinical response will not be considered a failure
- When a subject met vital sign criteria and was discharged from hospital during the 24 hour period of stability confirmation, the time of achieving TTCR was defined as the initial time at which vital signs were resolved and not the time of hospital discharge.
- If the clinical response has not been achieved by study completion, TTCR will be censored at the last assessment date of vital signs.
- If the subject did not achieve a clinical response the reason for censoring will be summarized (i.e. did not achieve vital sign resolution or reason for prematurely discontinuing the study).

Time to Respiratory Response (TTRR)

- Time to Respiratory Response defined as the first time meeting below, for at least 24 hours:
  - Return to pre-morbid oxygen requirement (subjects with chronic oxygen use), OR
  - Need for supplemental oxygen (administered by any modality – ventilator, non-invasive ventilation, facemask, facetent, nasal canula, etc) to no need for supplemental oxygen, OR
  - Respiratory rate >24/min and no supplement oxygen at baseline, and post baseline respiratory rate ≤24/min (without supplemental oxygen)
- Subjects who meet the above criteria at baseline (i.e., normal respiratory response) will not be included in the Kaplan Meier analysis and these subject not be considered as "improved" in the response rate
- If the symptoms have not resolved at Day 45, it will be censored at Day 45.

11.6.5. Biomarker

11.6.5.1. Biomarkers and Source

SAM	Serum	Nasal Wash	BAL
IL-6, IL-10, IP-10, IL-8, MPO, NE, IL-1b	Procalcitonin	IL-6, IL-10, **IP-10**, **IL-8**, **MPO, NE,** IL-1b	IL-6, IL-10, **IP-10**, **IL-8**, **MPO, NE,** IL-1b
	C1M, C3M, EL-NE	**Neutrophil Cell Counts**	
SP-D, sRAGE,	**SP-D, sRAGE**	**SP-D, sRAGE**	**SP-D, sRAGE**

Biomarker

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

AUC of Biomarker

- The area under the curve (AUC) to Day 5, Day 45, and PT Day 3 of biomarker as measured by the level of biomarker from biomarkers source;
- The AUC will be calculated as

$$AUC\ (0\text{-Day } x) = \sum_{0\text{-}l}\{½(C_i+C_{i+1})(t_{i+1}-t_i)\}$$

Where,

C_i = level of biomarker at actual time point i in Day

t_i = actual time of assessment for time point i in Day

i = actual time of assessment in Day (e.g. Day 1, 3, 5, 8, 16, 24, 32,day 45)

l = last i (Day 5, Day 45, or PT Day 3)

- Actual study day will be used for the AUC calculation.
- When baseline value of a biomarker is missing, AUC for the biomarker will be missing.
- When a subject has only baseline value, AUC will be missing.
- When value of a biomarker is missing between visits, there will be no imputation for the missing value, e.g. subject has day 1, 3, 5, 8, 16, 32, 45 values, and day 24 value is missing, day 24's value will not be imputed, AUC will be calculated using day 1,3,5, 8,16, 32, and 45 values.
- When value of a biomarker is missing at the end, last observation carried forward (LOCF) will be used to impute missing value, e.g, subject has day 1, 3, 5, 8, 16, 24, 32 values and day 45 is missing, day 45 value will be imputed using day 32 value (day 45 value will be assumed the same as day 32 value).
- The value of the AUC(0-45) biomarker is missing if there is no assessment beyond week 24.
- The length of time from Baseline to PT Day 3 visit will vary for subjects who prematurely discontinue the study and so the biomarker will also vary.

11.6.6. Health Outcomes

The FLU-PRO Total score is computed as a mean score across all 32 items comprising the instrument. Total scores can range from 0 (symptom free) to 4 (very severe symptoms).

Six domain scores are also computed, representing symptom severity in each of the following body areas: Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal, and Body/Systemic. Each domain score is calculated as the mean of all items comprising the domain. Each FLU-PRO domain score also ranges from 0 to 4. Algorithms and instructions for computing scores for the FLU-PRO Total and domain scores (including rules for handling missing data) are provided below:

Domain	Items	Scoring	Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items within **Nose** domain	3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items within **Throat** domain	2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items within **Eyes** domain	2 of 3 items must be present to calculate domain score
Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items within **Chest/Respiratory** domain	5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache How many times did you vomit? How many times did you have diarrhea?	Arithmetic mean of 4 items within **Gastrointestinal** domain	3 of 4 items must be present to calculate domain score
Body/Systemic	Headache Head congestion Felt dizzy Lack of appetite Sleeping more than usual Body aches or pains Weak or tired Chills or shivering Felt cold Felt hot Sweating	Arithmetic mean of 11 items within **Body/Systemic** domain	8 of 11 items must be present to calculate domain score

Total	All above 32 items	Arithmetic mean of all 32 items within FLU-PRO	In the presence of missing data, the above conditions for the calculation of all domain scores must be met in order to calculate the FLU-PRO total score.

11.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as a subject who completed the Day 45 assessment. • Withdrawn subjects will not be replaced in the study. • All available data from subjects 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.

11.7.2. 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 : o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.

11.7.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will not be imputed. • The recorded partial date will be displayed in listings.
Adverse Events, Exposure	• No missing data is expected for AE and EX. • Data Management will query any missing date of AE or EX.

11.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Time to Clinical Resolution	• For the primary analysis, a Discontinuation=Failure approach will be used (see Section 7.1.2). This approach handles two types of missing data: o due to subjects who prematurely discontinued the study o sporadic missing vital sign assessments

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Laboratory parameter will be graded according to the Division of AIDS (DAIDS) toxicity scales (protocol Section 12.5).

11.8.2. ECG

The following subdivision will be used to summarize the absolute and increase from baseline QTc interval data, and absolute PR interval by category

.

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>450 to ≤480	msec
Absolute QTc Interval	>480 to ≤500	msec
Absolute QTc Interval	>500	msec
Increase from Baseline QTc	>30 to ≤60	msec
Increase from Baseline QTc	>60	msec
Absolute PR interval	210-250	msec
Absolute PR interval	>250	msec

11.8.3. Vital Signs

Due to patient population, vital signs will not be flagged as potential clinical importance.

11.9. Appendix 9: Examination of Covariates, Subgroups & Other Strata

11.9.1. Examination of Covariates, Subgroups & Other Strata

Given the small number of subjects, no subgroups will be assessed.

11.10. Appendix 10: Multiple Comparisons & Multiplicity

11.10.1. Handling of Multiple Comparisons & Multiplicity

There will be no adjustments for multiplicity.

11.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

11.11.1. Statistical Analysis Assumptions

Not applicable

11.12. Appendix 12 – Abbreviations & Trade Marks

11.12.1. Abbreviations

11.12.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
RELENZA

Trademarks not owned by the GlaxoSmithKline Group of Companies
Captisol
FluPRO
KATZ ADL
SAS
Tamiflu

11.13. Appendix 13: List of Data Displays

11.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Biomarker	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic / Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Health Outcome	8.1 to 8.n	8.1 to 8.n
Virology	9.1 to 9.n	9.1 to 9.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

11.13.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 14: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Biomarker	BM_Fn	BM_Tn	BM_Ln
Pharmacodynamic / Biomarker	BMPD_Fn	BMPD_Tn	BMPD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln
Health Outcomes	HO_Fn	HO_Tn	HO_Ln
Virology	VR_Fn	VR_Tn	VR_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.13.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
DL	Data Look (blinded dry run)
IA	Interim Analysis Statistical Analysis Complete
HL	Headline
SAC	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

11.13.4. Study Population Tables

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Subject Disposition				
1.1.	ITT-E	ES1	Summary of Subject Disposition	
1.2.	ITT-E	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	
Protocol Deviation				
1.3.	ITT-E	DV1	Summary of Important Protocol Deviations	
Population Analysed				
1.4.	All Subjects Screened	SP1	Summary of Study Populations	
Demographic and Baseline Characteristics				
1.5.	ITT-E	DM1	Summary of Demographic Characteristics	Add age groups <35, 35-<50, >=50 and < 65, >=65. Add BMI and BMI categories <=20, 20-<=25, 25-<=30, 30-<=35, 40-<=45,>45 . Add tobacco use.
1.6.	ITT-E	DM5	Summary of Race and Racial Combinations	
Prior and Concomitant Medications				
1.7.	ITT-E	POP T2	Summary of Prior Exposure to Oseltamivir	Add a footnote “Only influenza therapies taken within 7 days of baseline visit were collected” CMPRIOR=’Y” or if medication started prior to IP start.No imputation for missing values

Study Population Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
1.8.	ITT-E	CM1	Summary of Prior Anti-influenzaTherapy	Includes pre-treatment CMs used for Anti-influenza therapy. Study team to review & provide list of CM terms prior to DBR Add a footnote "Only influenza therapies taken within 7 days of baseline visit were collected"
1.9.	ITT-E	CM1	Summary of Post-Treatment Anti-influenzaTherapy	Consider post-treatment as those records where the conmed start or end date are after the IP end date. Apply same logic for Table 1.11
1.10.	ITT-E	CM1	Summary of Pre-Treatment Steroids Use by Duration of Time	Add a column for "Pre-Treatment Steriod Use' Add a footnote "Only influenza therapies taken within 7 days of baseline visit were collected" the steroid use will be grouped as 3 categories, <1 week, 1 week – <6 months and 6 months and more, the table will summarize the number and percent of subject in each group
1.11.	ITT-E	CM1	Summary of Post-Treatment Steroid Use	
Other				
1.12.	ITT-E	POP T3	Summary of Flu Type and Symptoms	Includes influenza subtypes
1.13.	ITT-E	MH4	Summary of Past and Current Medical Conditions	By 'Past', 'Current', 'No'
1.14.	ITT-E	POP T4	Summary of Ventilation Status at Baseline	
1.15.	ITT-E	POP T6	Summary of Exposure to Study Treatment	
1.16.	IPP	POP T4	Summary of Ventilation Status at Baseline	

11.13.5. Efficacy Tables

Efficacy Tables				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Efficacy				
2.1.	IPP	EFF T2	Summary of Improved Clinical Response	
2.2.	IPP	EFF T6	Summary of Improved Respiratory Response	
2.3.	IPP		Summary of Post Baseline Ventilation Status	Mock per IVZ
2.4.	IPP	CM1	Summary of Frequency of Associated Antibiotic Use for Treatment of Complications of Influenza	List will be identified by study team prior to unblinding

11.13.6. Efficacy Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
2.1.	IPP	EFF F1	Individual Plot of Time to Clinical Response	10 lines for 10 subjects with different symbols representing event or censoring and different color representing different treatment.

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
2.2.	IPP	EFF F1	Individual of Time to Respiratory Response (Improved Respiratory Status)	10 lines for 10 subjects with different symbols representing event or censoring and different color representing different treatment, including any subject who resolved prior to baseline (negative response time, with a footnote).

11.13.7. Safety Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
3.1.	Safety	SAFE T1	Summary of All Adverse Events by System Organ Class and Maximum Grade	Please add a footnote to indicate “Mild or Grade 1”, “Moderate or Grade 2”, “Severe or Grade 3”, “Grade 4”.
3.2.	Safety	AE3	Summary of All Adverse Events by Overall Frequency	
3.3.	Safety	AE3	Summary of Grade 2-4 Adverse Events by Overall Frequency	
3.4.	Safety	AE3	Summary All Drug-Related Adverse Events by Overall Frequency	
3.5.	Safety	AE1	All Non-Serious Adverse Events by SOC and PT	Eudra
3.6.	Safety	AE16	SAE with number of subjects and number of occurrences by SOC and PT	Eudra
3.7.	Safety	AE3	Summary of Drug-Related Grade 2-4 Adverse Events by Overall Frequency	
3.8.	Safety	AE3	Summary of Adverse Events of Special Interest by Overall Frequency	AE terms for AESI will be provided prior to unblinding.
3.9.	Safety	AE8	Listing of Adverse Events for Subjects with Neutropenia (>= Grade 1)	
3.10.	Safety	AE3	Summary of Non-Fatal Serious Adverse Events	

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
3.11.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class	
3.12.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class	
3.13.	Safety	AE3	Summary of Drug-Related Non-Fatal Serious Adverse Events	
3.14.	Safety	AE15	Summary of Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	
3.15.	Safety		Summary of Maximum Treatment Emergent Toxicities of All Lab Parameters	IDMC output
3.16.	Safety	SAFE T2	Summary of Data Supporting Safety Halting Criteria	
3.17.	Safety	LB1	Summary of Creatinine by Visit	
3.18.	Safety	LB1	Summary of Change from Baseline for Serum WBCs, % Neutrophils, and Absolute Neutrophils Counts, Creatinine, Liver Function Test	IDMC output
3.19.	Safety	LB1	Summary of Absolute Neutrophils Count by Visit	

11.13.8. Safety Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
3.1.	Safety		Individual Plot of Creatinine by Visit by Subject	
3.2.	Safety		Individual Plot of Absolute Neutrophils Count by Visit by Subject	Page per each subject with a vertical line on day of treatment discontinued, include treatment, sex, age, in addition to subject ID

11.13.9. Pharmacokinetic Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
4.3	PK	PK06	Summary of Derived Whole Blood Danirixin PK Parameters (non-transformed and log-transformed) by Treatment	
4.4	PK	PK01	Summary of Whole Blood Danirixin Pharmacokinetic Concentration-Time Data (insert units) by Treatment and Day	Replace (insert units) with unit of measure. Include all subjects

11.13.10. Pharmacokinetic Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
4.1	PK	PK20	Median (IR) Plot of Whole Blood Danirixin Concentration-Time Plot (Linear and Semi-Log) by Treatment	1. Include line for LLQ along with footnote defining LLQ value 2. Overlay Day 1, 3 and 5.
4.2	PK	PK20	Mean (SE) Plot of Whole Blood Danirixin Concentration-Time Plot (Linear and Semi-Log) by Treatment	1. Include line for LLQ along with footnote defining LLQ value 2. Overlay Day 1, 3 and 5.
4.5	PK	PK16a	Individual Whole Blood Danirixin Concentration-Time Plots by Subject (Linear and Semi-log)	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 Day 1, 3 and 5

11.13.11. Biomarker Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
5.1.	IPP	BM_F2	Individual Plot of Serum Biomarkers by Visit by Subject - Influenza Positive Population	spaghetti plot, one plot per biomarker per matrix. Subject ID and treatment group should be identifiable by color/symbol
5.2.	IPP	BM_F2	Individual Plot of Nasal Wash Biomarkers by Visit by Subject - Influenza Positive Population	spaghetti plot, one plot per biomarker. Subject ID and treatment group should be identifiable by color/symbol

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
5.3.	IPP	BM_F2	Individual Plot of Nasal SAM Strips Biomarkers by Visit by Subject - Influenza Positive Population	spaghetti plot, one plot per biomarker. Subject ID and treatment group should be identifiable by color/symbol
5.4.	IPP	BM_F2	Individual Plot of BAL Biomarkers by Visit by Subject - Influenza Positive Population	spaghetti plot, one plot per biomarker. Subject ID and treatment group should be identifiable by color/symbol

11.13.12. Pharmacodynamic / Biomarker Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
6.1.	IPP	BMPD_F3	Matrix Comparative Plot of Individual Scatter Plot of Biomarkers vs Biomarkers for Each Biomarker Source by Select Visits	One page per biomarker. The x on y axis will contain the 5 biomarkers: Serum, Nasal wash, Nasal SAM Strips, BAL Include the pearson's correlation coefficient and p-value on the graph. Use one color One page for Day 1, Day 5, Day 45, PT Day 3
6.2.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Serum Biomarkers vs. Time to Clinical Response - Influenza Positive Population	One page per biomarker. TTCR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTCR, AUC(0-45) vs TTCR, AUC(0-PT Day 3) vs TTCR , Different color for treatment. Include a regression line for each treatment group
6.3.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Serum Biomarkers vs. Time to Respiratory Response - Influenza Positive Population	One page per biomarker. TTRR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTRR, AUC(0-45) vs TTRR, AUC(0-PT Day 3) vs TTRR , Different color for treatment. Include a regression line for each treatment group
6.4.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Nasal Wash Biomarkers vs. Time to Clinical Response - Influenza Positive Population	One page per biomarker. TTCR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTCR, AUC(0-45) vs TTCR, AUC(0-PT Day 3) vs TTCR , Different color for treatment. Include a regression line for each treatment group

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
6.5.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Nasal Wash Biomarkers vs. Time to Respiratory Response - Influenza Positive Population	One page per biomarker. TTRR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTRR, AUC(0-45) vs TTRR, AUC(0-PT Day 3) vs TTRR , Different color for treatment. Include a regression line for each treatment group
6.6.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Nasal SAM Strips Biomarkers vs. Time to Clinical Response - Influenza Positive Population	One page per biomarker. TTCR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTCR, AUC(0-45) vs TTCR, AUC(0-PT Day 3) vs TTCR , Different color for treatment. Include a regression line for each treatment group
6.7.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve Nasal SAM Strips Biomarkers vs. Time to Respiratory Response - Influenza Positive Population	One page per biomarker. TTRR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTRR, AUC(0-45) vs TTRR, AUC(0-PT Day 3) vs TTRR , Different color for treatment. Include a regression line for each treatment group
6.8.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve BAL Biomarkers vs. Time to Clinical Response - Influenza Positive Population	One page per biomarker. TTCR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTCR, AUC(0-45) vs TTCR, AUC(0-PT Day 3) vs TTCR , Different color for treatment. Include a regression line for each treatment group
6.9.	IPP	BMPD_F1	Individual Scatter Plot of Area Under the Curve BAL Biomarkers vs. Time to Respiratory Response - Influenza Positive Population	One page per biomarker. TTRR on y axis, AUC biomarker on x axis. AUC(0-5) vs TTRR, AUC(0-45) vs TTRR, AUC(0-PT Day 3) vs TTRR , Different color for treatment. Include a regression line for each treatment group

11.13.13. Pharmacokinetic / Pharmacodynamic Tables

Not Applicable

11.13.14. Pharmacokinetic / Pharmacodynamic Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
7.12	IPP		Target Engagement Biomarker versus DNX PK Parameters	Target engagement biomarkers include IL-8, MPO, neutrophil elastase and neutrophil counts (the one from nasal wash, not the one from blood)

11.13.15. Health Outcome Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
8.1.	IPP	HO T2	Summary of Change from Baseline in KATZ ADL Score and each ADL Activity	Includes baseline value
8.2.	IPP	HO T5	Summary of FLU-PRO Total and Domain Scores	Use “Baseline” for label instead of “Baseline for CFB”
8.3.	IPP	HO T5	Summary of Change from Baseline FLU-PRO Total and Domain Scores	Includes baseline value

11.13.16. Virology Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
9.1.	IPP	VR T1	Summary of Change from Baseline in Influenza Viral Load by qRT-PCR (log 10 VP/mL) Overall	Includes baseline value Summarize by A and B combined
9.2.	IPP	VR T2	Summary of Change from Baseline in Influenza Viral Load by qVC (log10 TCID50/mL) for Subjects Culture Positive at Baseline –Nasopharyngeal	Includes baseline value
9.3.	ITTE	VR T7	Proportion of Subjects with Other Co-infected Viruses by Multiplex RT PCR.	
9.4.	IPP	VR T4	Summary of Resistance Associated Mutations Detected in the NA Gene by Subtype - Nasopharyngeal	
9.5.	IPP	VR T4	Summary of Resistance Associated Mutations Detected in the HA Gene by Subtype - Nasopharyngeal	

11.13.17. Virology Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes
9.1.	IPP	VR F1	Individual Plot of Change from Baseline in Influenza Viral Load by qRT-PCR (log10 VP/mL) by Subject for Influenza A and B - Nasopharyngeal	Include zero at baseline
9.2.	IPP	VR F1	Individual Plot of Change from Baseline in Influenza Viral Load by qVC (log10 TCID50/mL) for Subjects Culture Positive at Baseline -Nasopharyngeal	Include zero at baseline

11.13.18. ICH Listings

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
Subject Disposition				
1.	All Subjects Screened	ES7	Listing of Screen Reasons for Screen Failure	
2.	ITT-E	ES2	Listing of Reasons for Study Withdrawal	
3.	ITT-E	SD2	Listing of Reasons for Study Treatment Discontinuation	
4.	ITT-E	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	
5.	ITT-E	TA1	Listing of Planned and Actual Treatments	
Protocol Deviations				
6.	ITT-E	DV2	Listing of Important Protocol Deviations	
7.	ITT-E	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	
Populations Analysed				
8.	All Subjects Screened	SA3a	Listing of Subjects Excluded from Any Population	
Demographic and Baseline Characteristics				
9.	ITT-E	DM2	Listing of Demographic Characteristics	
10.	ITT-E	DM9	Listing of Race	

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
11.	ITT-E	CM2	Listing of Concomitant Medications	Add column to indicate 'complications of influenza'
12.	ITT-E	MH2	Listing of Past and Current Medical Conditions	
13.	ITT-E	MH2	Listing of Subjects with Renal Impairment	Renal impairment is based on Creatinine Clearance Criteria Any time during study including baseline and post baseline
14.	IIT-E	CM2	Listing of Subjects with Prior Oseltamivir Exposure	
Exposure and Treatment Compliance				
15.	Safety	EX3	Listing of Exposure Data	
Adverse Events				
16.	Safety	AE8	Listing of All Adverse Events	Add asterisk for subjects with baseline renal impairment
17.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	
18.	Safety	AE8	Listing of Adverse Events of Special Interest	
Serious and Other Significant Adverse Events				
19.	Safety	AE8	Listing of Fatal Adverse Events	
20.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	
21.	Safety	SAFE L1	Listing of Reasons for Considering as a Serious Adverse Event	Use study 201682 as a reference

ICH : Listings				
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**
22.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study	
23.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment`	
24.	Safety	MH2	Listing of Subjects with Liver Stopping Events	
All Laboratory				
25.	Safety	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Concern (Grade 3-4)	
26.	Safety	LB5	Listing of All Laboratory Data	
ECG				
27.	Safety	CP_EG3	Listing of All ECG Values for Subjects with a Value of Potential Clinical Importance	
28.	Safety	CP_EG5	Listing of Abnormal ECG Findings	

11.13.19. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Need for early terminated study**
Population					
29.	ITT-E	POP L1	Listing of Flu Type and Symptoms		
30.	ITT-E	POP L2	Listing of Chest X-Ray Results	Indicate if subject is included in IPP	
Efficacy					
31.	IPP	EFF L1	Listing of Time to Clinical Response		
32.	IPP	EFF L2	Listing of Time to Respiratory Response		
33.	IPP		Listing of Vital Signs		
34.	IPP		Listing of Ventilation Status – Mechanical Ventilation	Use NAI114373 as a reference Add start and stop times	
35.	IPP		Listing of Ventilation Status – Supplemental Oxygen	Use NAI114373 as a reference Oxygen saturation history should be included in this listing	
36.	IPP		Listing of Hospital Discharge	Include date, duration and reason	
37.	IPP		Listing of Subjects Who Were Admitted to Intensive Care Unit		
Safety					
38.	Safety	LB5	Listing of Absolute Neutrophils for Subjects with Grade 3-4 Absolute Neutrophils or AE of Neutropenia		
39.	Safety	LB5	Listing of Creatinine for Subjects with Creatinine Increase > 0.5 mg/dl in Two Consecutive Visits		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Need for early terminated study**
PK					
40.	PK	PK L1	Listing of Whole Blood Danirixin Pharmacokinetic Concentration Data	Include NQ values	
41.	PK	LPK2	Listing of Whole Blood Danirixin Derived Pharmacokinetic Parameters		
Biomarker					
42.	ITT-E		Listing of Serum Biomarkers		
43.	ITT-E		Listing of Nasal Wash Biomarkers		
44.	ITT-E		Listing of Nasal SAM Strips Biomarkers		
45.	ITT-E		Listing of BAL Biomarker		
Virology					
46.	ITT-E	VR L1	Listing of Influenza Viral RNA (qRT-PCR and TCID50) in Nasopharyngeal	Use study 201682 as a reference	
47.	IPP	VR L2	Listing of Co-infected Subjects		
48.	ITT-E		Listing of Other Viruses by Multiplex RT PCR.		
49.	ITT-E		Listing of Phenotypic IC50 Results	Use NAI114373 as a reference	
50.	IPP		Listing of Resistant Mutations in NA and HA Genes	Use NAI114373 as a reference	
Health Outcome					
51.	IPP	HO L1	Listing of Hospital Readmission		
52.	IPP	HO L2	Listing of ADL KATZ Score and each ADL Activity		
53.	IPP	HO L3	Listing of 3-Point Scale (Bed Rest, Limit Ambulation, Unrestricted)		

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Need for early terminated study**
54.	IPP	HO L4	Listing of FLU-PRO Total and Domain Scores		

11.14. Appendix 14: Example Mock Shells for Data Displays

The mock shells for data displays are contained in a separate document.