TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	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
Development Phase	IIB
Effective Date:	12-JUL-2016

Author(s): PPD

SPONSOR SIGNATORY:

PPD

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Project Physician Leader

July 12, 2016
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND 121591; EudraCT 2016-002512-40

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201023

Rationale

Seasonal influenza affects 5-10% of the world's population annually, causing 3-5 million severe infections and 250,000 – 500,000 deaths. While early therapy with antivirals decreases severity and duration of symptoms of influenza, there are no drugs that have demonstrated clinical efficacy in randomized clinical trials in this population. Current treatment guidelines for hospitalized influenza recommend neuraminidase inhibitors as standard of care therapy. Following infection by a respiratory virus, neutrophils are the most abundant cells that migrate to the lungs. Influenza studies in animals have demonstrated that therapeutic treatment with the combination of a C-X-C chemokine receptor 2 (CXCR2) antagonist and a neuraminidase inhibitor reduced lung neutrophils and showed trends for improvements in clinical scores, lung function and pathology with no evidence of worsening outcomes, including viral load.

This study is designed to investigate an anti-inflammatory agent, danirixin (DNX; GSK1325756) co-administered with an antiviral treatment oseltamivir (OSV) for treatment of patients hospitalized for influenza infection and will be the first study to evaluate the efficacy and safety of intravenous DNX in this population.

Objective(s)/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 saturation; and --Respiratory status/Heart Rate/Systolic BP (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

Objectives	Endpoints
	• 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 saturation
	• 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 Intensive care unit (ICU)
	• Frequency of ICU admission and readmission
	• Length of stay in the hospital
	• Rates of development of septic shock
	• Frequency of antibiotic use
	• Proportion of subjects with improvement in Ordinal scale of clinical efficacy over time :
	  • Death
	  • Mechanical vent
	  • In the ICU
	  • 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 electro

Objectives	Endpoints
	cardiogram (ECG) parameters
• To characterize the pharmacokinetics of IV DNX in subjects hospitalized for influenza	• Standard pharmacokinetic parameters for IV DNX (i.e. area under the curve [AUC], maximum observed concentration [Cmax], average concentration [Cavg].

Overall Design

This study is a 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 co-administered (in all groups) with standard of care antiviral treatment (open-label oral 75 mg OSV) for patients hospitalized with influenza.

An Independent Data Monitoring Committee (IDMC) will perform monitoring and reviews of available safety and efficacy data. In the first influenza season, the IDMC will review unblinded safety data across all study cohorts, after every approximately 10-20 subjects have completed the post-treatment (PT) Day 3 visit. Frequency of IDMC reviews in subsequent seasons will be determined based on safety results of the interim analysis.

Treatment Arms and Duration

Subjects will be randomized in a 2:2:1 ratio to receive:

- 15 mg FBE IV DNX +75 mg OSV;
- 50 mg FBE IV DNX+75 mg OSV; or
- IV DNX placebo+75 mg OSV

Treatment duration will be 5 days. The investigator may elect to continue open-label oseltamivir treatment. Follow up will continue until Day 45 for all subjects.

Type and Number of Subjects

The study will recruit adult patients with influenza infection requiring hospitalization. Influenza patients with conditions of respiratory failure requiring mechanical ventilation, chronic kidney disease, acute renal failure, sepsis, or hemodynamic instability are considered a more severe population.

A maximum of 300 subjects are planned to be enrolled in the study, depending on study dose changes implemented after each of two planned interim analyses. Interim analyses are planned after each influenza season if there are more than 75 subjects enrolled. Completion of enrolment in this study is expected to take multiple influenza seasons.

Analysis

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.

An adaptive design is employed that allows for dropping a dose at interim analyses. These interim analyses also allow for early stopping for futility or efficacy. Probability of success for efficacy will be calculated, defined as a statistically significant treatment effect (p-value<0.025 for hazard ratio of TTCR >1) in a future two-arm comparative superiority study with 300 subjects per arm, given observed data.

Exposure to study medication, measured by the number of days on study drug, will be summarized by treatment arm. The proportion of subjects reporting adverse events (AEs) will be tabulated for each treatment arm.

2. INTRODUCTION

GSK1325756 (danirixin; DNX) is a novel, potent, selective, and reversible antagonist of the C-X-C chemokine receptor (CXCR) 2 and has been shown to decrease neutrophil transmigration and activation to areas of inflammation. An intravenous (IV) solution for infusion is being developed as an anti-inflammatory agent for hospitalized influenza (IFV) patients. Clinical development of an oral formulation for the treatment of chronic obstructive pulmonary disease (COPD) has also commenced.

Severe viral respiratory tract infections can cause direct injury through cytopathicity as well as tissue damage through an excessive immune response [Garcia, 2010; Perrone, 2008]. Selective CXCR2 antagonists potentially maintain a balance between inhibiting excessive immune response while preserving antimicrobial function by only partially reducing neutrophils, selectively inhibiting CXCR2 over CXCR1 (CXCR1 is involved in neutrophil degranulation), and maintaining acquired humoral immunity and cell-mediated immunity [Jones, 1996; Hartl, 2007; Seiberling, 2013; GSK Document Number YM2010/00163/07].

2.1. Study Rationale

This study is designed to investigate an anti-inflammatory agent (DNX) co-adminstered with an antiviral treatment (OSV) for treatment of patients hospitalized for influenza infection.

Seasonal influenza affects 5-10% of the world's population annually, causing 3-5 million severe infections and 250,000 – 500,000 deaths [Hayward, 2014]. While early therapy with antivirals decreases severity and duration of symptoms of influenza, there are no drugs that have demonstrated clinical efficacy in randomized clinical trials in this population. Current treatment guidelines for hospitalized influenza recommend neuraminidase inhibitors as standard of care therapy.

Following infection by a respiratory virus, neutrophils are the most abundant cells that migrate to the lungs, and excessive migration has been demonstrated to cause lung damage through release of tissue-destructive enzymes and reactive oxygen species and formation of neutrophil extracellular traps [Narasaraju, 2011]. Respiratory neutrophil levels and/or their associated chemokines involved in recruitment are correlated with clinical symptom severity of influenza infection in humans [Taubenberger, 2008; Short, 2014; Hayden, 1998].

Influenza studies in animals have demonstrated that therapeutic treatment with the combination of a CXCR2 antagonist and a neuraminidase inhibitor reduced lung neutrophils and showed trends for improvements in clinical scores, lung function and pathology with no evidence of worsening outcomes, including viral load [GSK Document Number YM2010/00163/07]. In addition, nonclinical and clinical studies support the hypothesis that selective antagonism of CXCR2 has an acceptable safety profile [GSK Document Number YM2010/00163/07].

This will be the first study to evaluate efficacy and safety of intravenous DNX (GSK1325756) given with a standard-of-care antiviral, oral oseltamivir (OSV), for

treatment of patients hospitalized with influenza infection. An IV formulation of DNX, danirixin hydrobromide (DNX HBr) has been developed and will be used for treatment in this study, since parenteral administration would be a preferred mode of delivery of medication in this hospitalized population, especially in critically ill patients. In this document, the IV DNX HBr dose will be presented as the free base equivalent (FBE).

2.2. Brief Background

Danirixin free base (DNX-FB) has undergone a comprehensive non-clinical assessment, including 39-week dog and 26-week rat toxicology studies, during which no signals were observed that might preclude further assessment in clinical trials. DNX-HBr has undergone a 4-week rat bridging toxicity study, a 14 day mouse pre-oncogenicity study and a full non-clinical assessment of reproductive toxicology comprising rat and rabbit embryofetal development studies in addition to male and female rat fertility studies.

A summary of the nonclinical information for DNX-FB and DNX-HBr, including a list of nonclinical Pharmacodynamic, Pharmacokinetic & Product Metabolism and Toxicology studies completed to date is provided in Section 4 of the Investigator's Brochure (IB) [GSK Document Number YM2010/00163/07].

Across the COPD and IFV programs, the number of subjects exposed to DNX is approximately 270. Six phase 1 clinical studies in healthy volunteers (HV) have been completed using oral and IV DNX treatment and over 180 HV subjects have been treated with DNX (10-400 mg DNX). The HV studies initially utilized the FB oral (up to 400 mg) and IV formulations of DNX (up to 50 mg twice daily (BID) for 5 days or 100 mg single dose). Most recently, Study 201037 in elderly HV has used the oral HBr formulation of DNX (50 mg single dose). Study 201682/DAISI was a phase II placebo-controlled study in uncomplicated outpatient influenza subjects (N=45). Subjects were treated with 75 mg oral DNX or placebo (PBO) BID and 75 mg oral OSV or PBO BID for 5 days. Safety of DNX treatment in the IFV population is being studied in a staged manner. DAISI was conducted in an outpatient IFV population prior to this study which investigates DNX treatment in less severe hospitalized subjects, followed by critically ill hospitalized subjects this study (Study 201023; DAHLIA). In DAHLIA, the HBr formulation of DNX will be provided as an IV infusion. Further information is located in the Investigator's Brochure [GSK Document Number YM2010/00163/07].

3. OBJECTIVES AND ENDPOINTS

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 saturation; 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 saturation • 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

Objectives	Endpoints

	readmission
	• Length of stay in the hospital
	• Rates of development of septic shock
	• Frequency of antibiotic use
	• Proportion of subjects with improvement in Ordinal scale of clinical efficacy over time :
	  • Death
	  • Mechanical vent
	  • In the ICU
	  • 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 co-infection.	• Change in quantitative influenza viral load over time and change from baseline measured from nasopharyngeal swab samples and lower respiratory tract 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

Objectives	Endpoints
	change from baseline measured from nasopharyngeal swab samples and lower respiratory tract 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 relationship of IV DNX.	• PK exposure for DNX and pharmacodynamic 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

4. STUDY DESIGN

4.1. Overall Design

This study is a 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 co-administered (in all groups) with standard of care antiviral treatment (open-label oral 75 mg OSV) for patients hospitalized with influenza.

Subjects will be assessed for influenza with a rapid diagnostic test provided by GlaxoSmithKline (GSK) (such as next generation rapid antigen test, commercial reverse transcriptase-polymerase chain reaction [RT-PCR], molecular assay), or local influenza test. A confirmatory RT-PCR test will be done by the central laboratory. Following confirmation of influenza with a rapid-diagnostic test, and meeting all other eligibility criteria, subjects will enter the study. Subjects will receive one of two doses of DNX given as an IV infusion, twice daily. Enrollment of subjects will be in a 2:2:1 ratio of 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 OSV after 5 days of study treatment.

The study will begin with enhanced safety monitoring in sentinel cohorts, leading to step-wise enrollment of subjects. Subjects will be enrolled based on increasing levels of renal impairment (Section 4.1.1), and less severe hospitalized subjects will be enrolled prior to enrollment of a critically ill subjects (Section 4.1.2 and Section 4.3), as this is the first study conducted in the hospitalized population with severe influenza.

Approximately 100 subjects are targeted to be enrolled in the study in the first influenza season and up to 100 subjects are planned to be enrolled in each of two additional influenza seasons for a total of approximately 300 subjects in the study.

Pharmacokinetic analysis will be done in batches during the study to provide confirmation of exposure to DNX. Similarly, to obtain evidence of target engagement, nasal and/or endotracheal samples may be evaluated in batches to determine respiratory biomarker (neutrophil) patterns following treatment with DNX.

Interim analyses of efficacy and safety data will be conducted to confirm dose regimens for subjects in the remainder of the influenza seasons. The first interim analyses will occur after the first flu season if there are more than 75 subjects enrolled. Additional interim analyses may be performed after approximately 50-66% of subjects have been enrolled.

Four potential outcomes of the interim analysis include the following: (1) stop the study for safety reasons, (2) stop the study for futility or efficacy, (3) continue with one DNX dose arm, or (4) continue with the two original DNX arms. The Bayesian decision criteria with regards to TTCR together with other efficacy, pharmacokinetic (PK) and safety data will be provided to support decisions on dose selection and study stopping after each interim analysis.

An Independent Data Monitoring Committee (IDMC) will perform monitoring and reviews of available safety and efficacy data. In the first influenza season, the IDMC will review unblinded safety data across all study cohorts, after every approximately 10-20 subjects have completed the post-treatment (PT) Day 3 visit. Study halting and dose arm halting criteria have been designed to guide IDMC review and decisions (summarized in Section 10.8.1 and detailed in the IDMC charter). Frequency of IDMC reviews in subsequent seasons will be determined based on safety results of the interim analysis.

The final analysis will occur when both accrual and follow-up are complete for all subjects. Formal statistical decision rules of interim and final analysis for TTCR are defined in Section 9.

4.1.1. Sentinel Cohorts with Enhanced Safety Monitoring

Sentinel cohorts with enhanced safety monitoring will be enrolled as part of a step-wise enrollment of subjects with different levels of renal impairment and disease severity (less severe and critically ill, Section 4.3). Subjects in the sentinel cohorts will have more stringent eligibility criteria (baseline creatinine clearance criteria and exclusion of subjects with diabetes mellitus and chronic kidney disease). The IV DNX formulation developed for this study contains 750 mg β-Cyclodextrin Sulfobutylether (SBE-β-CD, Captisol) per 50 mg of GSK1325756 (free base equivalent [FBE]), to achieve the desired

5mg/mL concentration (FBE) and ensure DNX remains in solution when added to the IV saline bag. Captisol is renally cleared with the potential for accumulation in subjects with severe renal impairment. As such, this study includes enhanced monitoring to evaluate for renal function. Subjects in the sentinel cohorts will undergo serum creatinine, eGFR and urine output assessments twice a day for the treatment period. Additional enhanced monitoring will be based on disease severity, peripheral neutropenia and bacterial infections.

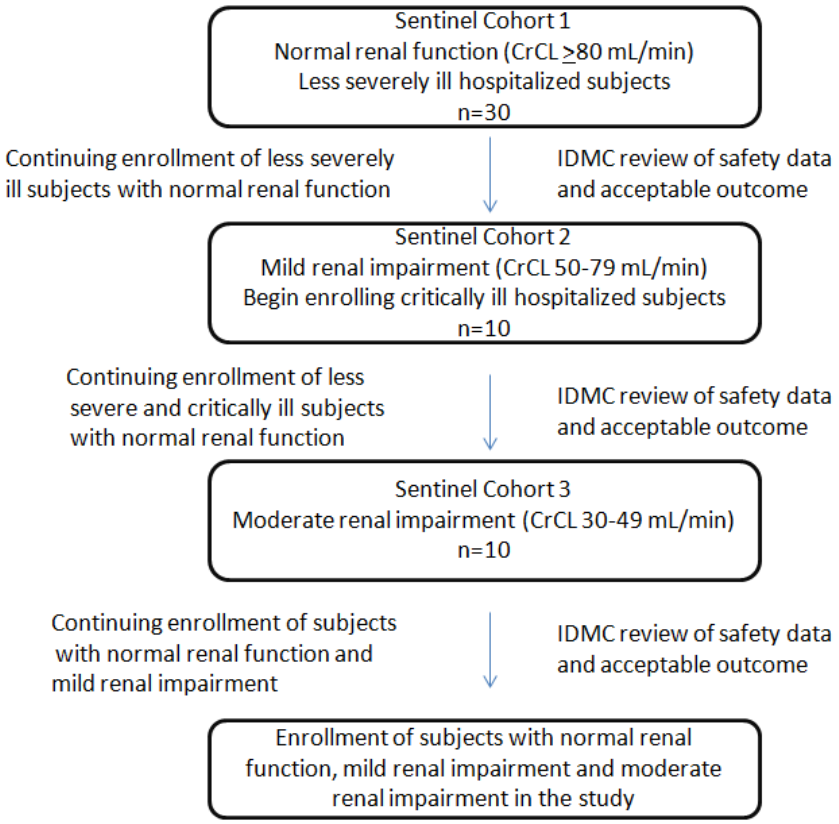
Approximately 30 subjects who are less severely ill and have baseline creatinine clearance within normal reference ranges (creatinine clearance ≥80 mL/min) will be enrolled in sentinel cohort 1 (Figure 1). The IDMC will first review available safety data after completion of the PT Day 3 visit, from approximately 10 subjects who are less severely ill and have normal renal function enrolled in sentinel cohort 1. Enrollment of subjects with normal renal function will continue during this review.

Following a review of all available data from the approximately 30 subjects in sentinel cohort 1, and an acceptable outcome from the IDMC, approximately 10 subjects with mild renal impairment, defined as baseline creatinine clearance of 50-79 mL/min will be enrolled in sentinel cohort 2, while continuing to enroll subjects with normal renal function in the study. At this stage, both less severely ill and the more critically ill subjects may be enrolled.

The IDMC will review the available safety data after completion of PT Day 3 from subjects in sentinel cohort 2 with mild renal impairment. Additional subjects with mild renal impairment will not be enrolled until the safety review is conducted by the IDMC, and the determination of an acceptable outcome.

Following an acceptable outcome from the IDMC review of the subjects with mild renal impairment, further enrollment of subjects with mild renal impairment will resume and approximately 10 subjects with moderate renal impairment (defined as baseline creatinine clearance of 30-49 mL/min) will be enrolled in sentinel cohort 3. The IDMC will review the available safety data after PT Day 3 from subjects in sentinel cohort 3 with moderate renal impairment. Following an acceptable outcome from the IDMC review, additional subjects with moderate renal impairment may be enrolled in the study.

Figure 1 Enrollment and Evaluation in Sentinel Cohorts



NOTE: CrCL = creatinine clearance

4.1.2. Safety Review Prior to Enrollment of Subjects with Severe Conditions at Baseline

The enrollment of critically ill hospitalized subjects will be delayed until IDMC review of the safety data from approximately 30 subjects considered to be less severe (Section 4.3).

The available safety data from subjects in this less severe population will be reviewed by the IDMC (unblinded) and GSK Safety Review Team (SRT) (blinded) after completion of study treatment. Enrollment of critically ill subjects (with normal renal function, and those with mild or moderate renal impairment) will only begin after an acceptable outcome is reported from the IDMC review of approximately 30 less severe subjects with normal renal function.

4.1.3. Study Design Change in the Event of Widespread OSV Resistance

A contingency study design is included in this protocol to facilitate rapid implementation of a global design change should widespread resistance to OSV occur during the course of the study.

If pre-defined criteria for widespread OSV resistance are met, OSV will be temporarily or permanently discontinued. Antivirals that are recommended at the time of OSV resistance will be provided as open-label treatment, and enrollment in the study will continue. The criteria for implementation of this study design change are:

- Evidence of substantial OSV resistance in circulating influenza viruses in participating countries in the relevant geographic areas reported by World Health Organization (WHO) or Centers for Disease Control (CDC), defined as ≥20% resistance in total of all circulating strains (e.g. ≥50% resistance in Pandemic Influenza A (H1N1) viruses which constitutes ≥20% of circulating strains), **OR**
- WHO or CDC recommend against treatment with single agent OSV.

In the absence of recommendations from WHO or CDC, other national health agencies in participating countries may recommend against treatment with single agent OSV for influenza treatment based on resistance patterns within a specific geographical area or country, or medical consensus. In these situations, a decision on whether to put enrollment on temporary hold at impacted site(s) should be made by investigators in consultation with local institutional review boards or ethics committees (IRB/IECs) and regulatory authorities.

While rapid diagnostic tests are not widely available to determine influenza strain or resistance, some study sites will have access to local laboratories with these capabilities that could allow appropriate subjects to continue to be enrolled.

The OSV arm may be re-instated if the level of OSV resistance diminishes below the criteria defined in the protocol, and if it is appropriate to do so, based on predicted patterns of circulating influenza strains.

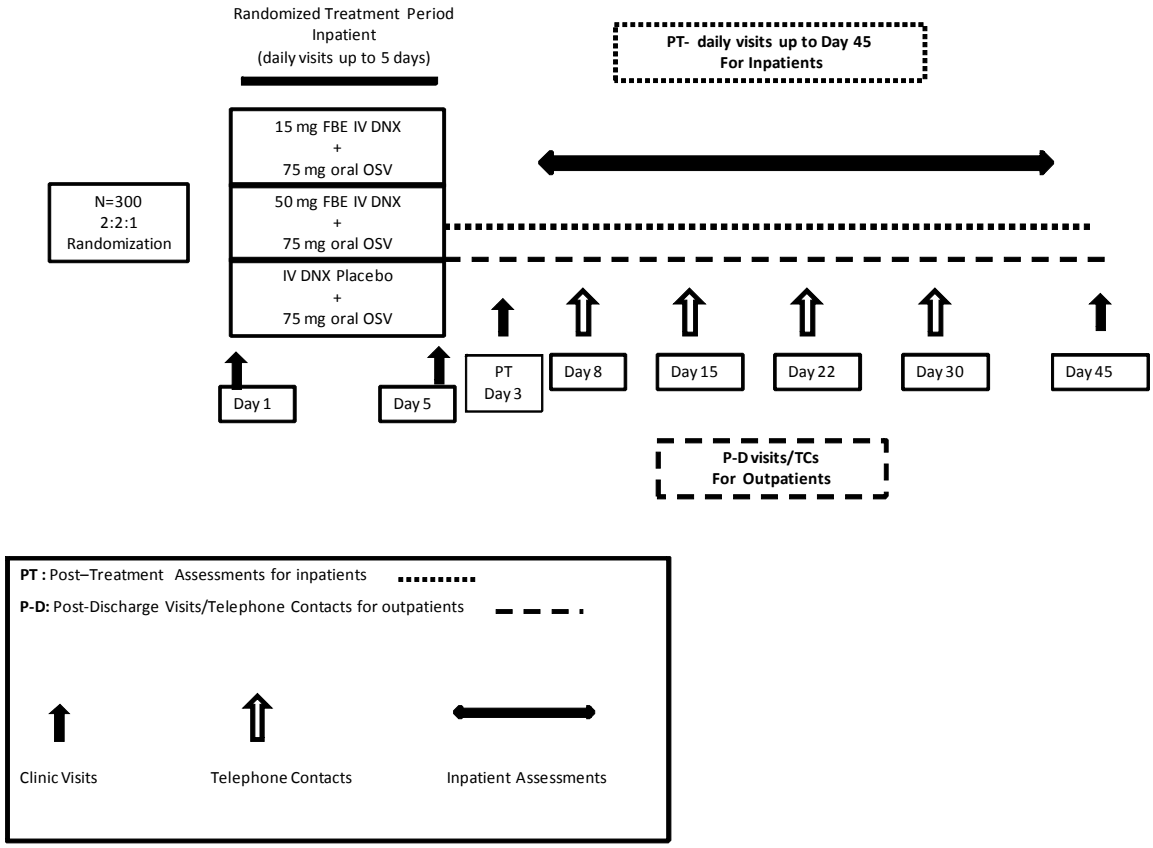
4.2. Treatment Arms and Duration

Subjects will be randomized in a 2:2:1 ratio to receive:

- 15 mg FBE IV DNX BID +75 mg OSV BID;
- 50 mg FBE IV DNX BID + 75 mg OSV BID; or
- IV DNX placebo BID + 75 mg OSV BID

Treatment duration will be up to 5 days (Figure 2). The investigator may elect to continue open-label oseltamivir treatment. If a subject is discharged from the hospital in less than 5 days, treatment with IV DNX will discontinue, irrespective of whether the investigator elects to continue oral OSV treatment at discharge. Follow up will continue until Day 45 for all subjects.

Figure 2 Study Schematic



4.3. Type and Number of Subjects

The study will recruit adult patients with influenza infection requiring hospitalization. Influenza patients with conditions of respiratory failure requiring mechanical ventilation, chronic kidney disease, acute renal failure, sepsis, or hemodynamic instability are considered a more severe population.

For the purposes of safety monitoring, the definitions below will be used.

Less severe hospitalized subjects are those who (but not limited to):

- are hemodynamically stable;
- may require oxygenation with facemask, facetent, nasal canula, etc;
- may or may not have radiological signs of lower respiratory tract disease; or
- may have exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), or other cardiovascular conditions not leading to hemodynamic compromise.

Critically ill hospitalized subjects are those who (but not limited to):

- require CPAP (i.e. new use for respiratory distress and not for chronic purposes such as sleep apnea), BIPAP, mechanical ventilation;
- have hemodynamic instability (with or without pressor support); or
- have central nervous system involvement (eg encephalopathy, encephalitis).

A maximum of 300 subjects are planned to be enrolled in the study, depending on study dose changes implemented after each of two planned interim analyses. The first interim analyses will occur after the first flu season if there are more than 75 subjects enrolled. Additional interim analyses may be performed after approximately 50-66% of subjects have been enrolled. Completion of enrolment in this study is expected to take multiple influenza seasons in the case of no early stopping for futility or success, with a total enrollment of approximately 300 subjects.

4.4. Design Justification

This will be the first study conducted with DNX in the hospitalized influenza population. As such the study design includes stepwise enrolment of sentinel cohorts with more stringent eligibility criteria as well as enhanced safety monitoring to assess the safety and tolerability of DNX. Following acceptable outcomes from IDMC reviews, additional subjects will be enrolled in the study.

The IV formulation of the HBr salt of DNX has been developed as treatment in this study, because parenteral administration would be a preferred mode of delivery in this hospitalized population.

All treatment groups in this study will receive open-label OSV, one of the recommended antiviral treatments for this population hospitalized for influenza [CDC, 2011; WHO, 2010]. One treatment group will receive matching IV DNX placebo as a double-blind control, while receiving open label OSV.

The primary composite endpoint of Time to Clinical Resolution (TTCR) was considered following guidelines developed by the Food and Drug Administration (FDA) for treatment of seriously ill hospitalized patients with influenza. While efficacy endpoints have not been definitively validated for all types of influenza trials, TTCR incorporates FDA guidance for inclusion of clinical signs and symptoms [FDA Guidance for Industry, 2011].

A key efficacy endpoint for this study is Time to Respiratory Resolution (TTRR) and is being evaluated as a secondary endpoint. Because DNX's mechanism of action is expected to be predominantly localized to the lung, TTRR will be analyzed to assess if it is a more relevant physiological measure. In this first study with DNX (co-administered with OSV) in hospitalized influenza, safety assessments are also a key secondary endpoint.

In alignment with the mechanism of action of DNX as an anti-inflammatory agent, which impacts the host response and not as a direct-acting antiviral, virologic endpoints are

being evaluated as exploratory endpoints. Additional exploratory endpoints include biomarkers (important in influenza infection and to demonstrate target effect) and health outcomes.

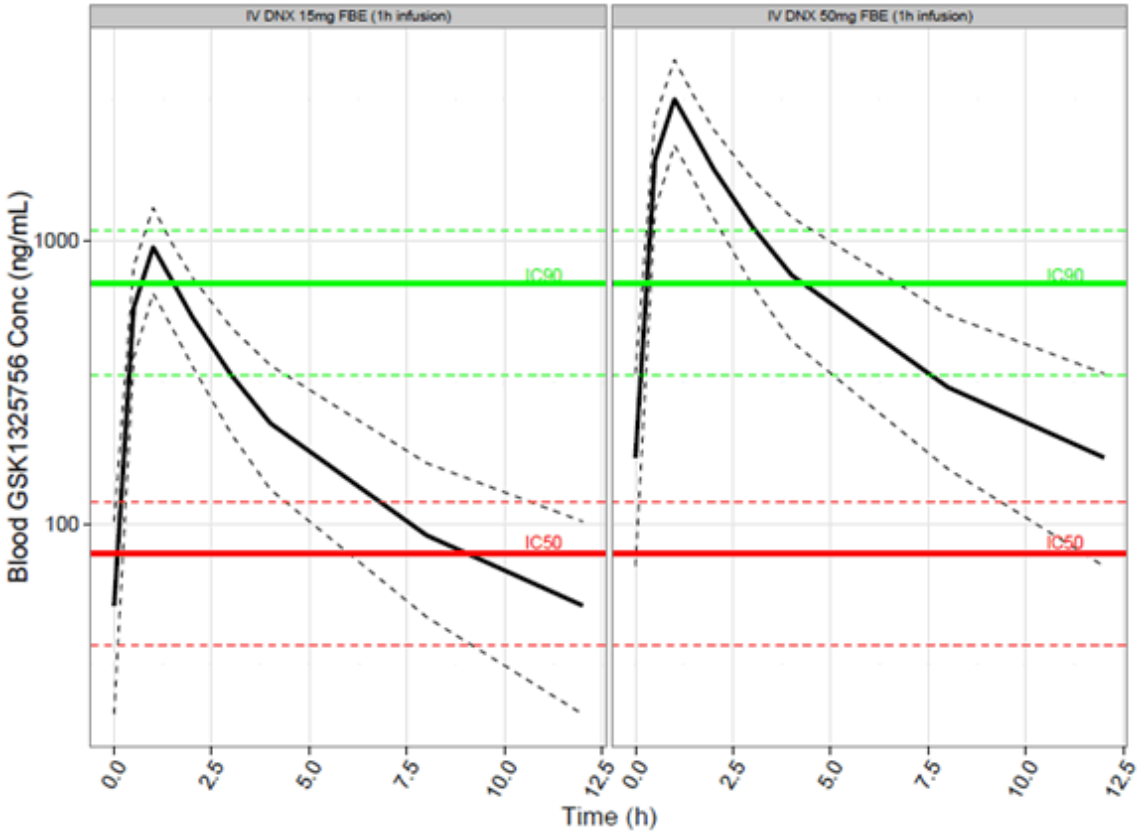
4.5. Dose Justification

Two doses of DNX are proposed for evaluation in this study. The proposed doses are 15 mg and 50 mg FBE, administered twice daily as a 1 hour IV infusion.

The doses for investigation are within the clinical experience of IV DNX in healthy subjects. Clinical exposure limits will be based upon NOAEL/2 for testicular toxicity, aligned with written responses received from the United States (US) FDA's Division of Pulmonary, Allergy, and Rheumatology Products in July 2013 for GSK's development of DNX in COPD. The projected systemic exposures for both of the selected doses in DAHLIA fall below the NOAEL/2 exposure for testicular toxicity. In Study 201022 (safety, tolerability and pharmacokinetics study in healthy subjects), DNX administered as the FB formulation was well tolerated and had an acceptable safety profile, as single doses of 10 mg (1h infusion), 25 mg (1h infusion) and 100 mg (2h infusion) and as twice daily repeat doses of 25 mg and 50 mg IV infusions (given over 1 hour) for 5 days (Section 5.3.1, DNX Investigator's Brochure). When DNX was administered as the FB tablet in Study 201682 (acute uncomplicated influenza subjects), no safety concerns were identified.

In Figure 3 the projected DNX concentration-time profile at steady-state for the proposed IV doses is shown with overlay of IC50 and IC90 for the sigmoidal PK/pharmacodynamic (PD) relationship between blood concentrations of DNX and their effect on C-X-C chemokine ligand (CXCL)-1 induced CD11b activated neutrophil levels in ex vivo blood samples (direct surrogate for CXCR2 antagonism) observed for healthy subject data pooled from Studies CX3112483 and CX3114922 (Table 4; DNX Investigator's Brochure Section 5.2.6). The data demonstrate that projected DNX levels for 15 mg and 50 mg exceed the IC90 (707 ng/mL) value for on average 1 and 4 hours respectively over the dosing interval. The projected DNX blood concentrations averaged over the 12 hour dosing interval will achieve concentrations in the region of IC70 and IC90, and at trough IC40 and IC70 for 15 mg and 50 mg respectively. A level of 50-70% CXCL1-induced CD11b expression has been associated with reduction of migration of neutrophils into the lungs in preclinical inflammation models and in human experimental medicine ozone challenge studies with a related CXCR2 antagonist, elubrixin (SB-656933) [Lazaar, 2011].

Figure 3 Projected Steady-state Concentration-Time Profile Over a Dosing Interval for IV DNX DNX-HBr FBE 15mg and 50mg with Overlay of IC50 and IC90 for CXCL-1-induced CD11b-activated Neutrophil Levels in Ex Vivo Blood Samples by DNX



NOTE: solid line=median population prediction; dashed lines=90% prediction interval; Projected DNX levels derived from a PK model defined for the IV data from Study 201022 (healthy subject PK study), where steady-state is projected to be reached within 3 days of repeat BID dosing, with minimal accumulation.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DNX can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK 1325756		
Reduction in Peripheral Blood Neutrophils	Peripheral neutropenia has been reported in clinical trials of other irreversible CXCR2 antagonists MK-7123 [Seiberling, 2013], SCH527123 [Nair, 2012] and AZD5069 [Kirsten, 2015]. Reduction in peripheral blood neutrophils may occur after a single dose. Peripheral blood neutrophils return to baseline approximately 24 to 48 hours after withdrawal of the CXCR2 antagonist.	Refer to the Time and Events Table (Section 7.1) for neutrophil monitoring. Peripheral blood neutrophil count of <1.0 x Gi/L is an exclusion criterion. Also, any subject that has a peripheral blood neutrophil count of <0.5 × Gi/L at two successive measures, will be withdrawn from IP and monitored until the neutrophil count returns to pre-dose levels.
Infection Risk	Neutrophils are an important component of host defense and innate immunity. Inhibition of neutrophil migration and activation could impact host defense and innate immunity and increase the risk of bacterial super- infection or worsening influenza virus-mediated disease.. Nonclinical studies in mice and ferrets with two CXCR2 antagonists in the same chemical class as DNX have not shown an increase in influenza viral load [GSK Document Number YM2010/00163/07] Secondary bacterial infections after viral infection have not been directly evaluated in nonclinical studies.	The site will monitor adverse events, complications of influenza (such as pneumonias [bacterial, ventilator, hospitalized and community], pneumothorax, pleural effusion, ARDS, myositis, encephalitis, myocarditis, bacterial bronchitis, otitis media, sepsis, sinusitis, bacteremia) and frequency of new associated antibiotic use and clinical symptoms of subjects during treatment and post-treatment. Also chest x-ray will be obtained at baseline for clinical comparison throughout treatment. Subjects will be discontinued from IP if develop significant worsening of symptoms or strong

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		suspicion or confirmation of progressive secondary bacterial infections or require antibiotics. In addition, the study has halting criteria that are part of the IDMC review.
Testicular Effects and Male Fertility	Testicular effects were observed in preclinical studies in mice, rats and dogs. Findings in rats at ≥150 mg/kg/day DNX or 500 mg/kg/day DNX HBr and dogs at 30 mg/kg/day DNX included spermatid degeneration, seminiferous tubular degeneration and secondary epididymal changes after 4 weeks of dosing with irreversible seminiferous tubule degeneration with oedema and atrophy following 26 weeks of dosing in rats. The male rat fertility study showed that the male rat fertility and gonadal function were affected without affecting libido or mating performance. No male-mediated fatal developmental toxicity was observed after 8 or 63 days of dosing. No adverse events related to testicular effects have been reported in clinical studies dosed up to 6 months to date. Short duration of treatment (5 days) in this study is considered to have low risk of the testicular effects.	Systemic exposure margins for the NOAEL for reproductive effects in male rats are 15- and 50-fold from the projected mean clinical systemic exposure (AUC) at a clinical BID dose of 15 mg DNX FBE and 50 mg DNX FBE, respectively, every twelve hours. Systemic exposure margins for the NOAEL for potential male-mediated developmental toxicity in rats are 57- and 191-fold from the projected mean systemic clinical exposure (AUC) at a clinical dose of 15 mg DNX FBE and 50 mg DNX FBE, respectively, every twelve hours. Systemic exposure margins for the NOAEL/2 for testicular effects in the 26 week rat toxicity study are 4- and 12-fold from the projected mean clinical systemic exposure (AUC) at a clinical BID dose of 15 mg DNX FBE and 50 mg DNX FBE, respectively, every twelve hours. For the short duration of treatment, this is considered sufficient to support the proposed clinical dosing regimen.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Renal Risk	The IV formulation of DNX contains Captisol that is renally cleared and has a potential for accumulation in renally impaired patients. Healthy volunteers have been dosed in a phase 1 study with an IV DNX formulation containing higher concentrations of Captisol with no safety concerns.	The study has intensive renal monitoring and stepwise inclusion of subjects with normal renal function followed by subjects with mild and then moderate renal impairment after review by an IDMC. The IDMC will include an ad hoc nephrologist member if there are 10 subjects across all treatment arms withdrawn due to the renal stopping criteria or if renal expertise is needed. Subjects with CrCl <30 mL/min will be excluded from the study. At the current doses, the Captisol concentrations in subjects with CrCl >30 mL/min are predicted to be below that obtained clinically with marketed Captisol containing IV voriconazole.

4.6.1.1. Oseltamivir Risk Assessment

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information is available in the local product label for oseltamivir.

Currently, there are no drugs that have demonstrated clinical efficacy in randomized clinical trials in the hospitalized influenza population. Twice daily 75 mg OSV is approved for treatment of uncomplicated acute influenza and is recommended for treatment in the hospitalized population, in the Infectious Diseases Society of America guidelines [Harper, 2009], guidelines from Centers for Disease Control and Prevention [CDC, 2011] and World Health Organization [WHO, 2010]. In the on-going Study 201682, oral 75 mg DNX and 75 mg OSV were co-administered to subjects with uncomplicated influenza, with no safety concerns identified to date.

4.6.2. Benefit Assessment

Currently, there is an unmet medical need for more effective treatments of viral lower respiratory tract infections (LRTI) requiring hospitalization. This study will provide an opportunity to determine if an anti-inflammatory drug with a novel mode of action may offer clinical benefit for the treatment of hospitalized influenza. This study follows an ongoing study of DNX alone or in combination with OSV in subjects with acute, uncomplicated influenza where no concerns have been identified to date.

In Phase I clinical trials to date and also in a phase IIa study in subjects with mild influenza who had co-administered OSV, all AEs (e.g. the most commonly observed AEs are headache and diarrhea) were mild-to-moderate in intensity in healthy subjects. In this study, the efficacy and safety of DNX co-administered with OSV will be evaluated in subjects hospitalized for influenza infections.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this Phase II clinical trial, the potential risks identified in association with GSK1325756/DNX are justified by the anticipated benefits that may be afforded to patients with severe viral respiratory tract infections.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure 2016; and oseltamivir prescribing information.

Written informed consent must be obtained from each potentially eligible subject or by an LAR for subjects who are incapable of consenting themselves such as those who are unconscious or due to their medical condition (e.g. too weak or debilitated, severe shortness of breath), prior to the initiation of any study procedures as outlined in this protocol. The consent form must have been approved by the Institutional Review

Board/Independent Ethics Committee (IRB/IEC). After signing an informed consent, subjects will complete assessments to determine subject eligibility. Each subject being evaluated for study enrollment will be assigned a subject number. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by GSK.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Adults 18 years (as per local laws) of age and older at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Presence of fever (≥38.0°C [≥100.4°F] by any route) at Baseline (enrollment) or history of fever/feverishness during the 48 hours prior.
3. O_2 saturation <95% on room air by trans-cutaneous method OR need for any supplemental oxygenation (non-invasive ventilation, facemask, facetent, nasal canula, etc) or ventilator support (mechanical ventilation, bi-level positive airway pressure [BIPAP], continuous positive airway pressure [CPAP]) or increase in oxygen supplementation requirement of ≥2 liters for subjects with chronic oxygen dependency. For those subjects with a history of chronic hypoxia (without supplemental oxygen), an oxygen saturation of at least 3% below the subject's historical baseline oxygen saturation. AND AT LEAST 2 out of the following 3: • Respiratory rate >24 breaths per minute. For those subjects who require ventilator support or oxygen supplementation, this requirement is waived. • Heart rate >100 bpm • Systolic bp <90 mm Hg.
4. Severity of symptoms at enrollment: • Less severe hospitalized subjects are those who (but not limited to): • are hemodynamically stable; • may require oxygenation with facemask, facetent, nasal canula, etc; • may or may not have radiological signs of lower respiratory tract disease; or • have exacerbation of underlying chronic disease, including asthma, chronic

obstructive pulmonary disease (COPD), or other cardiovascular conditions not leading to hemodynamic compromise.

- Critically ill hospitalized subjects are those who (but not limited to):
  - require CPAP, BIPAP, mechanical ventilation;
  - have hemodynamic instability (with or without pressor support); or
  - have central nervous system involvement (eg encephalopathy, encephalitis).

5. Presence of influenza that in the Investigator's judgment requires hospitalization for treatment and supportive care
6. Onset of influenza symptoms within 6 days prior to study enrolment. Symptoms may include cough, dyspnea, sore throat, feverishness, myalgias, headache, nasal symptoms (rhinorrhea, congestion), fatigue, diarrhea, nausea and vomiting.
7. A positive result from a rapid influenza test (provided by GSK) or other available, local laboratory diagnostic test;
8. Baseline renal criteria as follows:

Sentinel Cohorts:

- Normal renal function: Baseline creatinine clearance within normal reference ranges (≥80 mL/min) for the first approximately 30 subjects enrolled;
- Mild renal impairment: Baseline creatinine clearance of 50-79 mL/min for the next approximately 10 subjects enrolled into the sentinel cohort;
- Moderate renal impairment: Baseline creatinine clearance of 30-49 mL/min for the next approximately 10 subjects enrolled into the sentinel cohort.

Post-sentinel cohorts:

- Normal renal function, mild or moderate renal impairment: creatinine clearance >30mL/min.

9. Baseline Liver Function Tests as follows:

Liver parameter	**ALT≤5xULN**	**ALT>5 and ≤8xULN**	**ALT>8xULN**
Bilirubin ≤2x ULN	Include	Include only if bilirubin <1.5xULN	Exclude
Bilirubin >2x ULN	Exclude	Exclude	Exclude

SEX

10. Male or Female subjects could be eligible if :

Males:

Male subjects with female partners of child bearing potential must comply with the

following contraception requirements from the time of first dose of study medication until at least 36 hours (five half-lives) after the last dose of study medication.

a. Vasectomy with documentation of azoospermia.

b. Male condom plus partner use of one of the contraceptive options below:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]
- Contraceptive vaginal ring [Hatcher, 2007a]
- Percutaneous contraceptive patches [Hatcher, 2007a]

This is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009]."

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Females:

a. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented Bilateral Oophorectomy

b. Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

c. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6) from the first dose of study medication until at least 36 hrs after the last dose of study medication and completion

of the PT Day 3 visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
11. Subjects willing and able to give written informed consent to participate in the study and to adhere to the procedures stated in the protocol OR Legally acceptable representative (LAR) willing and able to give written informed consent on behalf of the subject to participate in the study for unconscious adults, and those incapable of consenting themselves due to their medical condition (e.g. too weak or debilitated, severe shortness of breath), due to literacy issues or included as permitted by local regulatory authorities, IRB/IECs or local laws.

COUNTRY-SPECIFIC
12. French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Subjects who, in the opinion of the investigator, are not likely to survive the next 48 hours beyond Baseline; 2. Immunosuppression, whether due to primary immunosuppressive conditions, such as history of inherited immunodeficiency syndromes, HIV infection, or secondary conditions, such as immunosuppressive medication, stem cell or solid organ transplantation, or malignancy; 3. Documented current liver disease (including Hepatitis A, B, or C), or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); 4. QTc Criteria: QTcB or QTcF >480 msec or >500 msec with bundle branch block; 5. For subjects enrolled in the sentinel cohorts: diabetes mellitus and chronic kidney disease; 6. Subjects who require dialysis, or are on renal replacement therapies; 7. Subjects who require extra corporeal membrane oxygenation (ECMO) at baseline (enrolled subjects who subsequently require ECMO may continue in the study) 8. Women who are pregnant as determined by a positive human chorionic gonadotrophin (hCG) ultrasensitive test prior to dosing or women who are

breastfeeding;

CONCOMITANT MEDICATIONS
9. Subjects who received other treatments for influenza including vitaglutam, umifenovir, and neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) for more than 72 hours during current acute illness; 10. Subjects who received any immunoglobulins within 6 months of screening or planned administration of any of these products during the treatment period. 11. Subjects treated with cytotoxic or immunosuppressive drugs within six months of study enrolment. Topical, intra-articularly injected, or inhaled glucocorticoids, topical calcineurin inhibitors or imiquimod are allowed.

RELEVANT HABITS
12. Known history of drug abuse within 6 months of study start.

CONTRAINDICATIONS
13. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
14. Absolute neutrophil count <1.0 Gi/L 15. Subjects who have participated in a clinical trial using an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

5.4. Withdrawal/Stopping Criteria

A subject is considered to be withdrawn prematurely from the study if they do not complete the Day 45 Visit.

Criteria for premature study withdrawal include:

- Adverse event
- protocol deviation
- non-compliance
- subject lost to follow up
- subject withdraws consent
- investigator discretion
- sponsor terminates the study

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Premature Discontinuation of Investigational Product

A subject is considered to have prematurely discontinued investigational product (IP) if they have not completed 5 days of randomized treatment (not applicable for subjects discharged from the hospital due to symptom improvement).

If a subject is prematurely discontinued from IP, the investigator must make every effort to perform all the remaining study visits as described in the Time and Events Table, including the final Day 45 Visit.

5.4.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

If any of the stopping criteria for parameters below are observed and confirmed, cessation of drug dosing and further evaluations will be instituted.

Liver Parameter	**ALT ≤10xULN**	**ALT >10xULN**
Bilirubin ≤2xULN	Continue	Discontinue IP
Bilirubin >2xULN (>35% direct)	Discontinue IP if ALT >5xULN, report as an SAE	Discontinue IP, report as an SAE

Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.3. Corrected QT Interval (QTc) Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and withdrawal from the study. This formula may not be changed or substituted once the subject has been enrolled.
    - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for withdrawal of this individual subject as well.
    - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety electrocardiograms (ECGs) and other non-protocol specified ECGs are an exception.

- The QTc stopping criteria should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

  A subject who meets either of the bulleted criteria below will be permanently discontinued from IP:

  - QTc >530 msec
  - Increase in QTcF or QTcB by more than 60 msec compared to baseline on two separate ECG tracings.

5.4.4. Other Stopping Criteria

Subjects should be permanently discontinued from IP if any of the following conditions are met:

- Serum creatinine: 0.5 mg/dL increase from baseline, on 2 successive readings;
- eGFR of <60 on two consecutive readings using the CKD-EPI calculation (eGFR of <30 for moderate renal impairment);
- Peripheral neutropenia: absolute neutrophil counts <0.5 Gi/L on 2 successive assessments.

5.5. Subject and Study Completion

A completed subject is one who has completed the Day 45 Assessment.

The end of the study is defined as the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

Completion of the trial globally is required in order to provide sufficient subjects as defined in Section 9.2, Sample Size Considerations.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Table 1 Characteristics of Study Treatments

	Study Treatment		
Product name: danirixin	GSK1325756	Placebo[1]	Oseltamivir[2]
Formulation description:	A sterile lyophilized powder containing GSK1325756H (hydrobromide salt hemihydrate) equivalent to 50mg of free base along with Beta-cyclodextrin sulfobutylether (Captisol), mannitol, citric acid and sodium hydroxide		Capsule: Grey/light yellow containing pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate Oral suspension: sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, saccharin sodium and water.
Dosage form:	Infusion	Infusion[1]	Capsules[2]
Unit dose strength(s)/Dosage level(s):	15 mg FBE; 50 mg FBE	N/A	75 mg
Route of Administration	For IV infusion	For IV infusion	Oral
Dosing instructions:	250 mL infusion	250 mL infusion	Dosing as per Prescribing Instructions
Physical description:	lyophilized powder/cake contained in a 30mL vial.	Clear solution	Capsules: grey/light yellow hard gelatin capsules. “ROCHE” is printed in blue ink on the grey body and “75 mg” is printed in blue ink on the light yellow cap. For Oral Suspension: Supplied as a white powder blend in a glass bottle.

	Study Treatment		
Product name: danirixin	GSK1325756	Placebo[1]	Oseltamivir[2]
Method for individualizing dosage:	Each vial is reconstituted with 9.5 mL water for injection and further diluted with saline for IV infusion	Saline for IV infusion[1]	Capsules. Available in blister packages of 10 Oral Suspension: After constitution, the powder blend produces a white tutti-frutti–flavored oral suspension. After constitution with 55 mL of water, each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL).
1 No vials of placebo to match IV DNX will be provided. A normal saline solution of matched volume will be prepared by unblinded personnel at the site to act as a placebo to DNX. 2 No oseltamivir capsules or powder for oral suspension will be provided. Sites will source the OSV locally and it will be provided open-label. OSV is manufactured by Roche Pharmaceuticals.			

6.1.1. IV IP and OSV Administration

6.1.1.1. Preparation of IV IP for Infusion

Unblinded personnel should prepare the IV IP infusion (DNX or matching PBO. Complete details on preparation of IV DNX will be provided in the pharmacy manual. The unblinded personnel should prepare a normal saline (0.9% sodium chloride) infusion for placebo to match IV DNX.

6.1.1.2. Preparation of OSV at the site

Details on preparation of oral suspension if needed for patients who are unable to swallow the capsules are available in the manufacturers prescribing information.

6.1.1.3. Administration of IV IP

IP infusion should be administered at a constant rate over approximately 1 hour (e.g. at an infusion rate of 250 mL/hour for a 250 mL infusion volume). Infusions should be given approximately 12 hours apart. If the first infusion of the day is administered after 12 noon, the next dose should be administered the following morning.

6.1.1.4. Administration of OSV

OSV dose is 75 mg to be administered twice daily for subjects who are able to swallow intact capsules. Dose adjustments of OSV (ie renal dosing) may be made as indicated in the prescribing information. For subjects unable to swallow intact capsules, qualified personnel may compound the appropriate dose of oseltamivir by opening capsules and pouring the contents of the capsules into a suitable small amount of sweetened food product such as sugar water, chocolate syrup, cherry syrup, dessert toppings to mask the bitter taste. The mixture should be stirred and the entire contents given to the subject.

The mixture must be swallowed immediately after its preparation [Tamiflu SPC, 2010]. Alternatively, the contents of the capsules can be made into suspension as per Tamiflu Prescribing Information or standard site procedures for administration via mouth, nasogastric, nasojejunal or gastrostomy tube. If the first dose of the day is administered after 12 noon, the next dose should be administered the following morning.

6.2. Treatment Assignment

Study treatment in this protocol refers to the blinded investigational drug IV DNX, IV DNX placebo and the open label oral OSV. Subjects will be assigned to 15 mg FBE IV DNX, 50 mg FBE IV DNX or IV DNX Placebo, in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen is provided in the table below:

Table 2 Treatment Regimens for Study 201023/DAHLIA

Treatment Arm	Sample Size per influenza season / study (3 infuenza seasons)	Treatment Label	Treatment Regimen[a]
A	40/120	15 mg FBE DNX	15 mg FBE IV DNX given twice daily with 75 mg oral OSV given twice daily
B	40/120	50 mg FBE DNX	50 mg FBE IV DNX given twice daily with 75 mg oral OSV given twice daily
C	20/60	PBO	IV DNX placebo given twice daily with 75 mg oral OSV given twice daily

a. OSV dose adjustments may be made as indicated in the prescribing information.

Subjects will be randomized using the RAMOS NG system. This system will be used by the investigator or designee to register the subject.

Details of how to use the RAMOS NG system to register and randomize subjects is provided in the study reference manual (SRM).

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. Minimization criteria will be based on influenza medication prior to hospitalization (Relenza, Tamiflu, peramivir or other), number of days of symptoms prior to hospitalization (0-3, 4-6), subject origin prior to hospitalization (nursing home, rehabilitation unit, home).

All randomized subjects will take investigational drug or matching placebo twice daily for up to 5 days in the hospital.

Once a randomization number has been assigned, it must not be re-assigned.

6.3. Planned Dose Adjustments

No pre-specified dose adjustments are planned in the first influenza season. Dose adjustments of OSV may be made as indicated in the prescribing information. Samples taken for PK analysis are planned to be analyzed during the study. Following the availability of the PK results sites will be informed if any dosing changes are to be made. Dose adjustments may also be determined following the IDMC review of safety data. Further details will be provided in the IDMC charter.

6.4. Blinding

This will be a double-blind study for the investigational product and both study staff and the subject will remain blinded to the investigational treatment. However, there will be qualified personnel at each study site who will be unblinded to allow preparation of study medication. Unblinding of GSK to the aggregated summary results by treatment group of the interim analyses is addressed in the IDMC charter.

The GSK team members will not have access to subject specific treatment assignment so as to not potentially introduce bias in discussions with the study center.

During the blinded randomized treatment period, subjects will receive an intravenous infusion (DNX or placebo) twice daily plus open label OSV oral therapy twice daily.

- IV infusion: Unblinded personnel will prepare an IV infusion of active DNX (15 mg FBE or 50 mg FBE) or normal saline infusion for each subject twice daily.
- Oral therapy: Qualified personnel will prepare the open-label oral oseltamivir therapy for each subject twice daily.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.

- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.

- The date and reason for the unblinding must be fully documented in the case report form (CRF).

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of 15 mg FBE IV DNX, 50 mg FBE IV DNX and IV DNX placebo will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of

unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

Subjects will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

15 mg FBE DNX, 50 mg FBE DNX and DNX placebo will be intravenously administered to subjects at the site.

Open label 75 mg OSV will be provided for oral administration by the investigator or designee to all subjects.

Administration will be documented in the source documents and reported in the CRF.

6.8. Treatment of Study IP Overdose

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator or treating physician should:

- contact the Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until IP can no longer be detected systemically (at least 3 days for IP)
- obtain a blood sample for pharmacokinetic (PK) analysis within 48 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis). PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.
- document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because currently the investigational medication is for acute treatment in the hospital and this is the first study evaluating efficacy and safety of IV DNX in subjects hospitalized for influenza.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Dietary Restrictions

- Subjects who use tobacco products will be allowed to take part, as long as they refrain from smoking for the duration of the hospitalization, but use of nicotine containing products will be recorded;
- Subjects should abstain from consuming alcohol for the duration of hospitalization.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

In general, concomitant medications (prescription and non-prescription) will be permitted during the study at the investigator's discretion (except for prohibited medications described in Section 6.11.2) and should be administered only as medically necessary during the study. All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, dates and times of administration are to be recorded.

6.11.2. Prohibited Medications and Non-Drug Therapies

The only approved antiviral drug permitted during the study is 75 mg OSV. All other approved or investigational influenza antiviral drugs are not permitted during the study (i.e. zanamivir, peramivir, laninamivir, amantadine, rimantadine, ribavirin, vitaglutam, umifenovir).

Immunosuppressive medications are prohibited during the treatment period including but not limited to rituximab, alkylating agents such as cyclophosphamide, nitrosoureas, platinum compounds; purine analogs such as fluorouracil; cytotoxic antibiotics such as dactinomycin, anthracyclines, mitomycin C, bleomycin, mithramycin.

Immunoglobulins are prohibited during the treatment period.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, biomarker or virological assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study for study assessments, including any extra study assessments that may be required.

7.1. Time and Events Table

Table 3 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
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								

	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]**	
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, 32, discharge or Day 45

	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]**	
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 4 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 sample)[l]	**X**					X
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.

7.2. Critical Baseline Assessments

- Demographic parameters to be collected include: year of birth, sex, race and ethnicity. Date and primary reason of hospitalization (influenza or not influenza related) will be recorded and if applicable, the date of intubation.

- Nasal swabs or nasopharyngeal sample will be taken for confirming an influenza infection. A rapid diagnostic influenza test will be provided by GSK or other local, validated laboratory test for influenza can be used.

- Vital signs to include temperature, heart rate, systolic and diastolic blood pressure, respiration rate, oxygen saturation. Oxygen delivery and ventilation status to be recorded approximately within approximately 1 hour prior to administration of the first dose of study medication;

- Influenza symptoms will be assessed at baseline prior to administration of study treatments. The presence of the following symptoms will be recorded: nasal symptoms (rhinorrhea, congestion), feverishness, cough, myalgias, fatigue, diarrhea, dyspnea, headache, sore throat, nausea and vomiting. The date of first onset of influenza like symptom(s) will also be recorded. The investigator or designee will assess and record influenza symptoms based on interview with the subject. In situations when subjects may not be able to communicate their symptoms, for example in subjects ventilated and/or sedated, the investigator or designee will record those signs/symptoms as 'unable to assess';

- Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at baseline.

- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

- Chronic underlying illness (including but not limited to asthma, COPD, diabetes, hypertension, Congestive Heart Failure) will be recorded.

- Pre-morbid functional status (defined as the best functional status in the 4 weeks prior to enrolment) and status at Baseline as measured by the Katz ADL scale and activity level (bed rest, limited ambulation or unrestricted) will be recorded in the eCRF. For subjects unable to communicate their pre-morbid functional status, this information should be requested from another close member of the household, close family member, or the subject's regular physician (if the subject has been under the care of a single physician for 3 months or longer).

- Laboratory evaluations:
    - Samples for clinical chemistry and hematology will be collected for analysis at a central laboratory (Table 7).
    - Samples for serum creatinine concentration, CBC with differential and liver function tests (LFTs) will also be obtained locally. The calculated creatinine clearance value will be recorded in addition to the serum creatinine concentration. Absolute neutrophil counts (ANC) and LFTs will be recorded.

- Nasopharyngeal swab to be collected prior to dosing for influenza subtype RT-PCR, qRT-PCR, quantitative culture and viral phenotype and genotype analysis and multiplex PCR.
- An endotracheal aspirate is requested only if the subject is intubated and a BAL sample is requested only if the procedure/sampling is being carried out for the routine management of the patient.
- Nasal Synthetic Absorption Matrix (SAM) strips will be used to collect samples from all subjects.
- An optional nasal wash procedure will be used for collecting samples and is requested from subjects who are not intubated;
- An ultrasensitive urine pregnancy test will be performed on women of childbearing potential;

- ECG: One baseline 12-lead ECG is required within approximately 24 hours prior to dosing. Any ECG that has been performed for clinical care can be utilized. A monitoring strip can also be utilized if a 12-lead ECG cannot be performed.

- Chest X-ray: Chest X-ray results (abnormal findings and normal findings) should be taken within 48 hours before the first dose of study medication and are to be recorded in the eCRF.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

Limited data will be collected on subjects who withdraw after providing informed consent but before initiation of treatment in the eCRF.

7.3. Efficacy

Clinical, virological and health outcomes assessments will be conducted as described in the Time and Events Tables Table 3, Table 4, to evaluate endpoint detailed in Section 7.3.3, Section 7.3.4, Section 7.3.5.

7.3.1. Primary Endpoint

The primary endpoint is time to clinical response (TTCR) (Table 5).

Clinical response is defined as resolution of at least 4 of the 5 signs described below within the respective resolution criteria, maintained for at least 24 hours, or hospital discharge, whichever comes first.

Table 5 Criteria for Time to Clinical Response

Sign of clinical response	Response criteria
Hospital discharge	Subjects who are discharged from hospital will be considered to have met the clinical response endpoint at the time of hospital discharge and are not required to have documented resolution of at least 4 response criteria (i.e. achieved success at the time of discharge if not observed prior to it).
OR	
Temperature[1]	≤36.6°C (≤97.9°F) – axilla, 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	• 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 (without supplemental oxygen)
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 measurements via a temporal artery thermometer, indwelling catheters and Swan Ganz catheters.

7.3.2. Secondary Efficacy Endpoints

- Time to Respiratory Response (TTRR): TTRR is defined as meeting at least one criterion below:
    - Return to pre-morbid oxygen requirement (subjects with chronic oxygen use or ventilator support), OR
    - Return to no requirement of supplemental oxygen, OR
    - Respiratory rate ≤24/min (without supplemental oxygen)

- Clinical measures of influenza illness will be evaluated as follows:
  - Time to absence of fever
  - Time to improved oxygen saturation
  - 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 and duration 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 associated antibiotic use
  - Proportion of subjects with improvement in Ordinal scale of clinical efficacy over time:
    - Death
    - Mechanical vent
    - In the ICU
    - Non-ICU hospitalization
    - Hospital discharge

7.3.3. Clinical Measures

- Vital Signs and Respiratory Status:
  - Temperature, heart rate, systolic and diastolic blood pressure and respiration rate will be assessed three times daily during hospitalization between approximately 8 AM to 8 PM. Three times daily assessments should be made at approximately the same time each day, morning, afternoon and evening, and at least 5 hours apart. Measurements will be made once at clinic visits post-discharge.
  - The following evaluations will be recorded for respiratory status: Oxygen saturation (by transcutaneous oximetry), modality and quantity of oxygen administration; duration of oxygen supplementation and method of support, with dates and times will be recorded for invasive methods such as BiPAP, CPAP (i.e. new use in the hospital for respiratory distress and not for chronic use such as for sleep apnea), and mechanical ventilation; and for non-invasive methods such as nasal canula, facetent facemask etc. Respiratory status will be assessed

three times daily during hospitalization between approximately 8 AM to 8 PM, and once daily at clinic visits post-discharge. Three times daily assessments should be made at approximately the same time each day, morning, afternoon and evening, and at least 5 hours apart.

- Influenza symptoms: The presence and severity of influenza symptoms (nasal symptoms (rhinorrhea, congestion), feverishness, cough, myalgias, fatigue, diarrhea, dyspnea, headache, sore throat, nausea and vomiting) will be recorded once daily during hospitalization. The investigator or designee will assess and record influenza symptoms based on interview with the subject at approximately the same time each day. In situations when subjects may not be able to communicate their symptoms, for example in subjects ventilated and/or sedated, the investigator or designee will record those signs/symptoms as 'unable to assess'.
- Development of septic shock will be assessed by occurrence of hypotension requiring vasopressive therapy and serum lactate level >2 mM after adequate fluid resuscitation [Shankar-Hari, 2016; Seymour, 2016; Singer, 2016]. Additional information will be provided in the SRM.
- The number of days in the hospital, date and time of ICU admission and discharge, if applicable, and date and time of hospital discharge will also be recorded.

7.3.4. Virologic Measures and Biomarker Sampling

Samples for virologic measures and biomarker sampling will be collected locally as in the Time and Events Tables (Section 7.1). These samples will include nasal swabs, nasopharygeal swabs, nasal samples (SAM strips and optional nasal washes), endotracheal aspirates (from intubated subjects), whole blood samples (ribonucleic acid [RNA] transcriptome analysis, deoxyribonucleic acid [DNA]), serum, and BAL samples from subjects where it is part of routine management. When multiple respiratory samples are to be taken at any visit, samples will be collected in the following order (Table 6).

Table 6 Sampling Order of Respiratory Samples for Virologic and Biomarker Assessments

Sequence of Collection	Sample Type	Study Day (inpatients)	Outpatient Assessments	Number and location of samples	Purpose
1	Nasal swab or nasopharyngeal swab	Day 1	N/A	Nare 1	Influenza diagnostic test
2	Nasal SAM strips	Day 1, 3, 5, 8, 16, 24, 32; also at discharge or Day 45	PT Day 3, Day 45	Both nares	Biomarker analysis
3	Nasopharyngeal swabs	Day 1, 3, 5, 8, 12, 16, 20, 24, 28, 32;	PT Day 3	Nare 2	Virology analysis
4	Nasal wash[a]	Day 1, 3, 5, 8, 16, 24, 32; also at discharge or Day 45	PT Day 3, Day 45	Both nares	Neutrophil counts/biomarker analyses
	Endotracheal samples[b]	Day 1, 3, 5, 8, 16, 24, 32, 45	N/A	ET aspirate	Neutrophil counts/biomarker analyses

a. Requested from subjects who are not intubated (optional procedure).
b. Required from subjects who are intubated.

- Nasal swabs will be collected at baseline to confirm influenza infection with a rapid influenza diagnostic test provided by GSK or other local test.

- Nasopharyngeal swabs will be collected for influenza Subtype RT-PCR, qRT-PCR, quantitative culture and may also be used for rapid influenza diagnosis. Nasopharyngeal samples will also be used for viral genotyping and phenotyping if needed and for multiplex PCR assay.

- Endotracheal (ET) aspirates will be collected from subjects who are intubated. The endotracheal samples will be used for biomarker evaluation and neutrophil counts (Section 7.6).

- Nasal SAM strips will be used to collect nasal samples and will be used for biomarker evaluation.

7.3.5. Health and Value Outcomes

Patient reported outcomes on intensity of influenza symptoms with the FluPRO [Powers 2016], impact of influenza on activities of daily living with the Katz ADL score [Katz 1970; Katz, 1983] and activity level (3 point scale –bed-rest, ambulatory, unrestricted), will be assessed with questionnaires during hospitalization and following discharge from the hospital. Readmission rates will be determined for discharged subjects who are readmitted to the hospital by Study Day 45.

The FluPRO, the Katz ADL Score and the Activity Level will be evaluated once a day during treatment. Flu PRO will also be measured once daily while in the hospital and once daily after discharge until Day 14. Other assessments times are specified in the Time and Events Tables (Section 7.1).

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests such as vital signs, physical exams and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The IDMC will perform reviews of unblinded safety data on a regular basis (Section 10.8.1). The GSK SRT will routinely review blinded safety data during the study.

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4 (Section 12.4)

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. Severity of AEs is to be reported as defined according to the Division of AIDS (DAIDS) table (Appendix 5, Section 12.5).

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4.1.5) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.1.5. AEs of Special Interest

The following disease related events are common in subjects hospitalized for influenza and can be serious/life threatening. These events will be considered as AEs of special interest (AESI):

- Pneumonias (bacterial, ventilator, hospitalized and community; guidelines for diagnosis [Mandell, 2007], [Niederman, 2005])
- Pneumothorax
- Pleural effusion
- ARDS
- Myositis
- Encephalitis
- Myocarditis
- Bacterial bronchitis
- Otitis media
- Sepsis
- Sinusitis
- Bacteremia

These events will be recorded on the AESI page in the subject's CRF. These AESIs will be monitored by the IDMC and the GSK SRT on a routine basis. Relevant medical tests and treatment, including antibiotics use, and clinical symptoms of subjects during treatment and post-treatment, will be recorded in all assessments for these events.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects and in female partners of male subjects will be collected after the start of dosing and until 3 days post last dose.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems ie assessment of the head, eyes, ears, nose, sinuses, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.4.4. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate.

7.4.5. Electrocardiogram (ECG)

Single (baseline) and triplicate (post-enrollment) 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3 for QTc stopping criteria and additional QTc readings that may be necessary.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments (Table 7) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional protocol-specified or non-protocol specified laboratory assessments performed at the institution's local laboratory result in a change in subject management

or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

For safety laboratory assessments, approximately 20 mLs of blood sample will be obtained at each visit. For laboratory parameters that will be assessed at the local laboratory for subject management as per the Time and Events Tables (Section 7.1), an additional approximately 20 mLs of blood sample will be obtained.

All study-required laboratory assessments will be performed by a central laboratory. In addition, CBC with differential (for evaluating neutropenia), LFTs and serum creatinine will also be measured by the local laboratory and used for subject management. Local laboratory values for neutrophils, serum creatinine and LFTs (aspartate transaminase, AST; alanine transaminase, ALT) will be recorded in the eCRF. These values will be utilized by the Investigator for subject management and by the IDMC prior to data from central laboratory being available.

- The results of each laboratory test that is considered clinical significant should be reported as an AE or SAE as applicable and must be entered into the eCRF.

NOTE: Additional local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the eCRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 7.

Table 7 Protocol Required Safety Laboratory Assessments

Central Laboratory Assessments/Approximate Volume per Assessment	**Parameters**			
Haematology/2 mL	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [a]/4.5 mL	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein

Central Laboratory Assessments/Approximate Volume per Assessment	**Parameters**			
	Glucose	Calcium	Alkaline phosphatise	Albumin
Other Screening Tests/17 mL	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • Ultrasensitive urine hCG Pregnancy test (for women of child bearing potential) at Baseline and Day 3 Post-treatment [b]			

a. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 2, Section 12.2.

b. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All laboratory tests with values that are considered clinically significantly abnormal should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

A blood sample (1-2 mL) for the provision of dried blood spot (DBS) collection and subsequent analysis of DNX concentration, will be collected at the time points indicated in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

Blood (DBS) analysis will be performed under the control of Platform Technology and Science – InVivo/ InVitro Translation PTS- IVIVT/ Third Party Resources TPR, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of DNX will be determined in blood (DBS) samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the blood has been analyzed for DNX any remaining blood may be analyzed for other compound-related metabolites and the results reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

7.6. Biomarker(s)/Pharmacodynamic Markers

Blood samples and serum separated for analysis (approximately 10 mL whole blood) will be collected at each time point indicated in Section 7.1, Time and Events Table for exploratory biomarker testing to identify biomarkers for neutrophil activation and accumulation, immune responses, inflammation, factors that may be associated with or influence influenza infection as well as biological and clinical responses to DNX treatment in combination with OSV. Exploratory markers may include but are not limited to interleukin-8 (IL-8), procalcitonin, respiratory neutrophil cell counts, neutrophil elastase, myeloperoxidase.

7.6.1. Novel Biomarkers

Nasal wash sample(s) may be collected from non-intubated subjects and endotracheal aspirates will be collected from intubated subjects during this study. Nasal samples will be collected from all subjects using SAM strips. Collected samples may be used for the purposes of measuring novel biomarkers to identify factors that may influence or be associated with influenza infection as well as the biological and clinical responses to DNX.

Samples will be collected at the timepoints indicated in Section 7.1. The timing of the collections may be adjusted on the basis of emerging pharmacokinetic or pharmacodynamic (PD) data from this study or other new information in order to ensure optimal evaluation of the PD endpoints.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with influenza or medically related conditions and/or the action of DNX may be identified by application of:

- RNA transcriptome analysis of whole blood samples;
- Protein biomarker analysis of the serum, endotracheal, BAL and/or nasal samples; and
- Cellular composition evaluation from the nasal, endotracheal and/or BAL samples.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

Analysis and reporting of these biomarkers may occur after issue of the full Clinical Study Report.

7.6.1.1. RNA Transcriptome Research

Transcriptome studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological and clinical response relating to influenza or the action of DNX.

The same samples may also be used to confirm findings by application of alternative technologies.

7.6.1.2. Proteome Research

Serum, endotracheal, BAL and/or nasal sample proteome studies may be performed by immunoassay, or an alternative equivalent procedure. Proprietary algorithms and standard statistical techniques, such as ANOVA and ANCOVA, may be used to identify individual proteins exhibiting statistically acceptable changes in their levels between samples, and between groups of samples. The levels of the proteins will be measured by immunoassay or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to influenza and medically related conditions, or the action of DNX.

The same samples may also be used to confirm findings by application of alternative technologies.

7.7. Genetics

Information regarding genetic research is included in Appendix 3 .

7.8. Viral Genotyping and Phenotyping

Samples for viral genotyping and phenotyping will be collected at time points indicated in the Time and Events Table (Section 7.1).

Resistance analyses will be carried out to investigate the occurrence of OSV resistance in circulating influenza viruses in participating countries. Phenotyping and genotyping (Neuraminidase and hemagglutinin sequencing) will be performed on nasopharyngeal swabs collected on Baseline/Day 1 and the last visit with detectable virus. Further visits may be analyzed if phenotype, genotype and viral load results indicate that resistance may be present.

Genotypic and phenotypic analyses will be carried out at a central laboratory.

Detailed information on sample handling, labeling, storage and shipment are provided in the SRM.

7.9. Value Evidence and Outcomes

Assessments for Patient Reported Outcomes will be done at time points indicated in the Time and Events Table (Section 7.1).

Exploratory endpoints of patient reported outcomes on intensity of influenza symptoms with the FluPRO [Powers, 2016], impact of influenza on activities of daily living with the Katz ADL score [Katz, 1970; Katz, 1983] and activity level (3 point scale –bed-rest, ambulatory, unrestricted), will be assessed with questionnaires during hospitalization and following discharge from the hospital. Readmission rates will be determined for subjects who are discharged from the hospital within 30 days post treatment.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The goal of the study is to assess the efficacy of twice daily 15 mg and 50 mg FBE IV DNX given with standard of care 75 mg oseltamivir twice daily, in hospitalized patients with influenza. The primary endpoint is the TTCR in subjects with confirmed influenza. TTCR and Clinical response is defined in Section 9.4.1.

A probability inference approach will be used for decision-making. A Bayesian predictive probability of success will be provided to support assessment of early stopping for futility and/or efficacy and for final efficacy. Observed data at interim analyses or final analysis of this study will be used to calculated predictive probability of success of a future study with larger sample size. Success is defined as a statistically significant treatment effect (p-value<0.025 for hazard ratio of TTCR >1) in a future two-arm comparative superiority study with 300 subjects per arm.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The TTCR endpoint was used in GSK Study NAI14373 (IV zanamivir), conducted in a similar population of hospitalized influenza subjects. The TTCR endpoint from NAI114373 was calculated as defined in the protocol. Median TTCR from Kaplan-Meier estimates in the oseltamivir treatment group from the confirmed influenza population are summarized (Table 8), and applied to the less severe subjects and for critically ill subjects at baseline separately. Hazard ratio estimates from the proportional hazard model of IV zanamivir vs oseltamivir range from 1.6 – 1.7 in the Mechanical ventilation at baseline sub-group in study NAI114373. Hazard ratio and clinical improvement in days over oseltamivir are provided in the table for reference.

Table 8 Hazard Ratio and Clinical Improvement over oseltamivir

Population	Median Recovery time (days)	Hazard Ratio	Clinical effect Improvement in Days
Less severe sub-population	5.8	1.2	1
		1.5	2
Critically ill sub-population	20.1	1.2	3.4
		1.5	6.7

TTCR is assumed to follow exponential distribution with constant hazard rate λ. To incorporate prior information on the oseltamivir arm, a weak informative prior of Gamma (4, 4/0.83) distribution with mean parameter of 0.83 and weight parameter of 4, will be used for λ in the oseltamivir arm. The mean and median hazard rates for the Gamma distribution are 0.83 and 0.76, respectively, with 2.5th percentile of 0.226 and 97.5th percentile of 1.819. A constant hazard rate of 0.83 for exponential distribution centers the recovery time at 5.8 days. A weight parameter of 4 provides relative small weight on the prior and will allow data to dominate the posterior, the 95% recovery time could range from 2.6 to 21.4 days to allow wide range possible outcomes. A non-informative prior will be used for DNX arms.

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 will enrol approximately 300 subjects with ratio 2:2:1 to 15mg IV DNX FBE+ OSV, 50mg IV DNX FBE + OSV and IV DNX placebo +OSV arms. An informative prior on the oseltamivir arm for the Bayesian analysis provides additional data from prior study for the control arms, combining prior data and data from this study allows us to have fewer subjects on the control arm with a 2:2:1 randomization ratio.

It is assumed that there is no difference in treatment effect between the less severe and severe population. Assuming a treatment effect of HR =1.5 for 50 mg of DNX FBE and

a clinically meaningful treatment effect of HR =1.2 for 15 mg of DNX FBE, there is an 82% chance that at least one dose will meet the success criteria described below:

At interim: Probability (success) >90%

Final: Probability (success)>50%

Assuming a HR of 1 for both doses, the overall type I error is 9%, i.e. there is a 9% chance of one or more doses being declared success incorrectly.

Table 9 Type I error by Interim and Overall

Hazard ratio	Type I error for Interim 1 n=100	Type I error for Interim 2 n=200	Overall Type I Error
Criteria	Probability (success) >90%	Probability (success) >90%	Probability (success) >50%
L: HR=1 H: HR=1	1%	0%	9%

9.2.2. Sample Size Sensitivity

In order to characterize and understand the performance of the design, the study was simulated under several different scenarios.

The powers for different scenario range from 45-90% and detail result are shown in Appendix 9.

Scenarios considered for the true hazard ratios for low dose and high dose DNX are shown in Table 10.

Table 10 Dose-Response profile for Hazard Ratio

	DNX FBE 15 mg + OSV	DNX FBE 50mg + OSV
1. No effect	1	1
2. Small effect	1.2	1.2
3. Large effect	1.5	1.5
4. Mixed effect	1.2	1.5
5. High dose large effect	1	1.5

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

An adaptive design is employed that allows for dropping a dose at interim analyses. These interim analyses also allow for early stopping for futility or efficacy. The target

sample size is 300 subjects; if early futility or efficacy criteria are met, as few as 75-100 subjects may be enrolled. The first interim analyses will occur after the first flu season if there are more than 75 subjects enrolled. Additional interim analyses may be performed after approximately 50-66% of subjects have been enrolled.

Assuming an effective drug (HR = 1.2 and 1.5 for low and high dose respectively), there is 26% probability, the sample size is 100 subjects at the end of the study, and 67% probability the sample is less than 220. Assuming an ineffective drug (HR =1 for both doses), there is 47% probability, the sample size is 100 subjects at the end of the study, and 86% probability the sample is less than 220. Average sample size for each Dose-response profile is provided in Appendix 9.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The Intent to Treat Exposed Population (ITT-E) will consist 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. The ITT-E population will be used for summaries of study population and disposition.

The Influenza positive population (IPP) will consist of all subjects in the ITT-E population with influenza infection (positive influenza PCR or culture at any timepoint) confirmed by central lab testing. Unless stated otherwise, the IPP will be used as the primary population for the primary efficacy analysis and all other efficacy analyses.

The safety population will consist of all randomized subjects who receive at least one dose of investigational product. Subjects will be assessed according to their actual treatment received, regardless of the randomization assigned. This will be the primary population for safety analysis.

The Pharmacokinetic population: This population includes all subjects who underwent blood PK sampling during the study and from whom one or more blood concentration is determined. This population will be used for listing of plasma concentration-time data, non-compartmental PK and population PK analysis, as data permit.

Per Protocol Population (PP): The PP population will exclude subjects from the IPP who have no post-baseline data or who have protocol deviations that lead to exclusion from PP population. To decide which subjects should be removed from PP population, the study team will review protocol deviation prior to unblinding of the data. If warranted, the Per Protocol population will be used for sensitivity analysis in the primary efficacy comparisons

9.3.2. Interim Analysis

An Independent Data Monitoring Committee (IDMC) will review key safety data from the sentinel cohorts. Enrollment in the study will continue during IDMC review. In the first influenza season, the IDMC will continue to review unblinded safety data, after

every approximately 10-20 subjects have completed treatment in the study. Frequency of IDMC reviews in subsequent seasons will be determined based on safety results of the interim analysis.

Pharmacokinetic analysis will be done in batches during the study with special emphasis to process and analyze after each sentinel group has completed treatment, to provide an early confirmation of exposure to DNX. Similarly, to obtain early evidence of target engagement, nasal wash and/or endotracheal samples may be evaluated in batches during the study to determine neutrophil patterns following treatment with DNX.

Interim analyses of efficacy and safety data will be conducted to confirm dose regimens for subjects in the remainder of the influenza seasons. The first interim analyses will occur after the first flu season if there are more than 75 subjects enrolled. Additional interim analyses may be performed after approximately 50-66% of subjects have been enrolled.

Detail of data to be reviewed and decision criteria will be included in the IDMC charter.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy

9.4.1.1. Primary Analysis

Probability of success, denoted Prob(Success), will be calculated. Success is defined as a statistically significant treatment effect (p-value<0.025 for hazard ratio of TTCR >1) in a future two-arm comparative superiority study with 300 subjects per arm, given observed data.

Let T_0 be the time to clinical response for the control arm with exponential distribution

$$T_0 \sim Exp(\lambda)$$

Where λ is the hazard rate constant of subjects in the control arm, the parameter is modeled as:

$$\lambda \sim Gamma(n, \frac{n}{\mu})$$

Where n is prior weight parameter and μ is prior mean parameter, we set n=4 and μ=0.83 based on the hazard rate observed in study NAI114373.

Let T_d be the time to clinical response for the dose level *d:*

$$T_d \sim Exp(h_d)$$

where $h_d = \lambda e^{\theta_d}$, and θ_d is log-hazard ratio and modeled with independent dose-dose response model.

Kaplan-Meier estimates for the median of TTCR for each treatment group and the median difference and 95% confidence interval (CI) between DNX arms and OSV will be provided.

9.4.1.2. Secondary Analyses

Median, median difference and 95% for the median differences between DNX arms and OSV for Time to respiratory response and each component of TTCR will be provided.

Proportion of subjects with clinical response, improved respiratory status and resolution of each component of TTCR over time will be summarized.

Proportion of subjects with improvement in Ordinal scale of clinical efficacy over time will be provided.

9.4.1.3. Subgroup Analyses

To evaluate the benefit of DNX in a sub-population, one key subgroup has been pre-specified for evaluation of efficacy.

- **Disease severity at baseline**: Patients requiring CPAP (i.e. new use for respiratory distress and not for chronic purposes such as sleep apnea), BIPAP, mechanical ventilation, those who have hemodynamic instability (with or without pressor support), or have central nervous system involvement (eg encephalopathy, encephalitis) are considered a more severe population.

Additional subgroups will be pre-specified in the reporting analysis plan.

The KM estimates for the primary analysis and key secondary analyses will be repeated by the subgroups.

9.4.2. Safety Analysis

All safety analyses will be based on the Safety Population defined in Section 9.3.1.

Exposure to study medication, measured by the number of days on study drug, will be summarized by treatment arm. The proportion of subjects reporting adverse events (AEs) will be tabulated for each treatment arm. The following summaries of AEs will be provided:

Incidence and severity of All AEs;

Incidence and severity of treatment related AEs;

Incidence and severity of AEs leading to withdrawal from study;

Incidence of serious AEs (SAEs).

Laboratory data, vital signs and ECG data (absolute values and change from Baseline) will be summarized by visit and treatment group. In addition, the maximum post-baseline toxicity grade will be tabulated by treatment.

9.4.3. Virology Analyses

Change from baseline in influenza viral load by qRT-PCR and by quantitative virus culture from nasopharyngeal swabs will be summarized and plotted by treatment and visit. Summary of proportion of subjects with no detectable influenza viral RNA by qRT-PCR and by quantitative virus culture from nasopharyngeal swabs.

9.4.4. PK and PK/PD Analyses

Blood concentration data will be listed and summarized by day, and planned sampling time in both tabular and graphical forms. Blood PK parameters will be listed and summarized by treatment.

A population-based PK model may be constructed based on the DNX PK data. Population PK analyses will be done under separate Population-PK Reporting and Analysis Plans.

Relationships between various blood DNX PK parameters and pharmacodynamic measures (e.g., TTCR, TTRR, clinical response, biomarkers, or safety measures) may be explored using simple correlation analyses or population-based PK/PD approach.

9.4.5. Other Analyses

The results of the biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the biomarker results.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study.

It is anticipated that many subjects who will be eligible for this study will not be able to give consent themselves due to their medical condition. In such cases, and if allowed by applicable local laws, consent may be obtained from a legally acceptable representative (LAR). The investigator and/or the sites IEC/IRB have responsibility for applying local laws in the matter of who has the capacity to consent and who qualifies as a LAR of a potential subject, or according to IRB/IECs and local laws in special situations where the subject may be included without consent beforehand by a LAR.

When appropriate, in addition to the consent provided by the LAR, subjects who are determined not to have the capacity to provide informed consent should be given information according to his/her capacity to understand and asked for their written assent to participate in the study.

Subjects enrolled in the study on the basis of consent by a LAR will be given the opportunity to provide written confirmatory consent when and if they become able to do so. If the subject declines to confirm consent they will be withdrawn from the study at the point where they decline consent.

- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.
- Definition of what constitutes source data can be found in the SRM

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.

- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

10.8.1. Independent Data Monitoring Committee

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The IDMC will meet at a minimum of approximately every 10-20 subjects during the first influenza season. Frequency of meetings for the subsequent seasons will be determined based on results of the interim analysis.

The IDMC will be provided guidelines on study halting criteria. While recommendations for stopping have been provided as a guide, the IDMC will base its recommendation to halt, or modify the study based on all available evidence. The guidance is not a substitute for the medical, scientific or statistical expertise of the IDMC body. Based on the data review, the IDMC will also determine whether a DNX dose needs to be dropped. While the IDMC will receive all available safety data, it is purported that, based on the mechanism of action of DNX, decisions will include comparison between treatment groups for parameters such as neutropenia, AESIs, SAEs, incidence of bacterial infections and disease progress. The details of the schedule of planned interim analyses and the analysis plan for IDMC review is described in the charter which is available upon request.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV	Atrioventricular
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BIPAA	Bilevel positive airway pressure
BMD	Bone mineral density
CDC	Centers for Disease Control
CI	Confidence Interval
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstruction Pulmonary Disease
CPK	Creatine Phosphokinase
CPAP	Continuous Positive Airway Pressure
CRF	Case report form
CXCL1	Chemokine (C-X-C motif) ligand 1
CXCR1	C-X-C Chemokine Receptor 1
CXCR2	C-X-C Chemokine Receptor 2
CV	Cardiovascular
CVA	Cerebral vascular accident
CYP	Cytochrome P450
DAIDS	Division of AIDS
DBS	Dried Blood Spot
DNA	Deoxyribonucleic Acid
DNX	Danirixin
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigiliance
GSK	GlaxoSmithKline
H1N1	Pandemic Influenza A Virus
HBsAg	Hepatitis B S antigen
hCG	Human Chorionic Gonadotrophin

Hep-B	Hepatitis B Virus
Hep-C	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HPLC	High performance liquid chromatography
IB	Investigator Brochure
IMB	Inter-menstrual bleeding
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITT-E	Intent to Treat Exposed Population
IL-8	Interleukin 8
INR	International Normalized Ratio
IP	Investigational Product
IPP	Influenza Positive Population
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally acceptable representative
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NOAEL	No Observed Adverse Effect Level
OSV	Oseltamivir
PBO	Placebo matching Danirixin
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per Protocol Population
PR	PR interval; duration in milliseconds from the beginning of P wave to onset of ventricular depolarization (R)
PTS-DMPK	Platform Technology and Science - Drug Metabolism and Pharmacokinetics
QRS	QRS interval; duration in milliseconds of the QRS complex, the deflections in an electrocardiographic tracing, representing ventricular activity of the heart
qRT-PCR	Quantitative Reverse Transcription – Polymerase Chain Reaction
QT	QT interval; duration in milliseconds between the Start of Q Wave and end of T Wave
QTc	Corrected QT interval

QTcB	Corrected QT Interval using Bazette's formula
QTcF	Corrected QT Interval using Fridericia forumula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAM	Synthetic Absorption Matrix
SRM	Study Reference Manual
TPN	Total parenteral nutrition
TTCR	Twice daily on time to clinical response
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
RELENZA

Trademarks not owned by the GlaxoSmithKline group of companies
Captisol
FluPRO
Katz ADL
Tamiflu

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping Criteria

Liver Parameter	**ALT ≤10xULN**	**ALT >10xULN**
Bilirubin ≤2xULN	Continue	Discontinue IP
Bilirubin >2xULN (>35% direct)	Discontinue IP if ALT >5xULN, report as an SAE	Discontinue IP, report as an SAE

Required Actions and Follow-up Assessments to Liver Stopping Criteria

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 3 days after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
	alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week) [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT>5x upper limit of normal (ULN) . Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT > 5xULN **and** bilirubin ≥2xULN (>35% direct bilirubin), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.3. Appendix 3 - Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Influenza susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for deoxyribonucleic acid (DNA) extraction. The blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample

destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

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12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease (influenza symptoms), unless judged by the investigator to be more severe than expected for the subject's condition.   • Influenza symptoms: nasal symptoms (rhinorrhea, congestion), feverishness, cough, myalgia, fatigue, diarrhea, dyspnea, headache, sore throat, nausea and

vomiting.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 5xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT > 10xULN.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy

- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and grade each AE and SAE according to the DAIDS toxicity scales (Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse

Events, Appendix 5).

- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- [If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.]
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the protocol contact:
    - SAE listing
    - Demographic listing
    - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.5. Appendix 5: Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Averse Events Version 1.0, December 2004; Clarification August 2009

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of $\leq$ 2 units packed RBCs (for children $\leq$ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated

PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hypertension					
	Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	**≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
	Correction: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to **≥** 180 from > 180 (systolic) and to **≥** 110 from > 110 (diastolic).				
	Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension		NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion		Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated

PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged PR interval					
	Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
	Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	1. Type I 2nd degree AV block	2. Type II 2nd degree AV block	Complete AV block
Prolonged QTc					
	Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
	Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism		NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)		Present without loss of consciousness	Present with transient loss of consciousness	NA	NA

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social and functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	Bone mineral density BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	Standard International Units are listed in italics			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 300 – 400/µL	200 – 299/mm^3 200 – 299/µL	100 – 199/mm^3 100 – 199/µL	< 100/mm^3 < 100/µL
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 0.600 x 10^9 – 0.650 x 10^9/L	500 – 599/mm^3 0.500 x 10^9 – 0.599 x 10^9/L	350 – 499/mm^3 0.350 x 10^9 – 0.499 x 10^9/L	< 350/mm^3 < 0.350 x 10^9/L
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 1.000 x 10^9 – 1.300 x 10^9/L	750 – 999/mm^3 0.750 x 10^9 – 0.999 x 10^9/L	500 – 749/mm^3 0.500 x 10^9 – 0.749 x 10^9/L	< 500/mm^3 < 0.500 x 10^9/L
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 1.250 x 10^9 – 1.500 x 10^9/L	1,000 – 1,249/mm^3 1.000 x 10^9 – 1.249 x 10^9/L	750 – 999/mm^3 0.750 x 10^9 – 0.999 x 10^9/L	< 750/mm^3 < 0.750 x 10^9/L
Infant*†, ≤1 day	4,000 – 5,000/mm^3 4.000 x 10^9 – 5.000 x 10^9/L	3,000 – 3,999/mm^3 3.000 x 10^9 – 3.999 x10^9/L	1,500 – 2,999/mm^3 1.500 x 10^9 – 2.999 x 10^9/L	< 1,500/mm^3 < 1.500 x 10^9/L
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL 1.00 – 2.00 g/L OR 0.75 – 0.99 x LLN	75 – 99 mg/dL 0.75 – 0.99 g/L OR 0.50 – 0.74 x LLN	50 – 74 mg/dL 0.50 – 0.74 g/L OR 0.25 – 0.49 x LLN	< 50 mg/dL < 0.50 g/L OR < 0.25 x LLN OR Associated with gross bleeding

12.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.6.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Contraceptive requirements for male subjects with female partners of reproductive potential (when applicable).

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until [at least five half-lives of study medication OR for a cycle of spermatogenesis following five terminal half-lives] after the last dose of study medication.

1. Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview.
2. Male condom plus partner use of one of the contraceptive options below that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label:
    - Contraceptive subdermal implant

- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011a]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.6.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication or be withdrawn from the study]
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.

- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

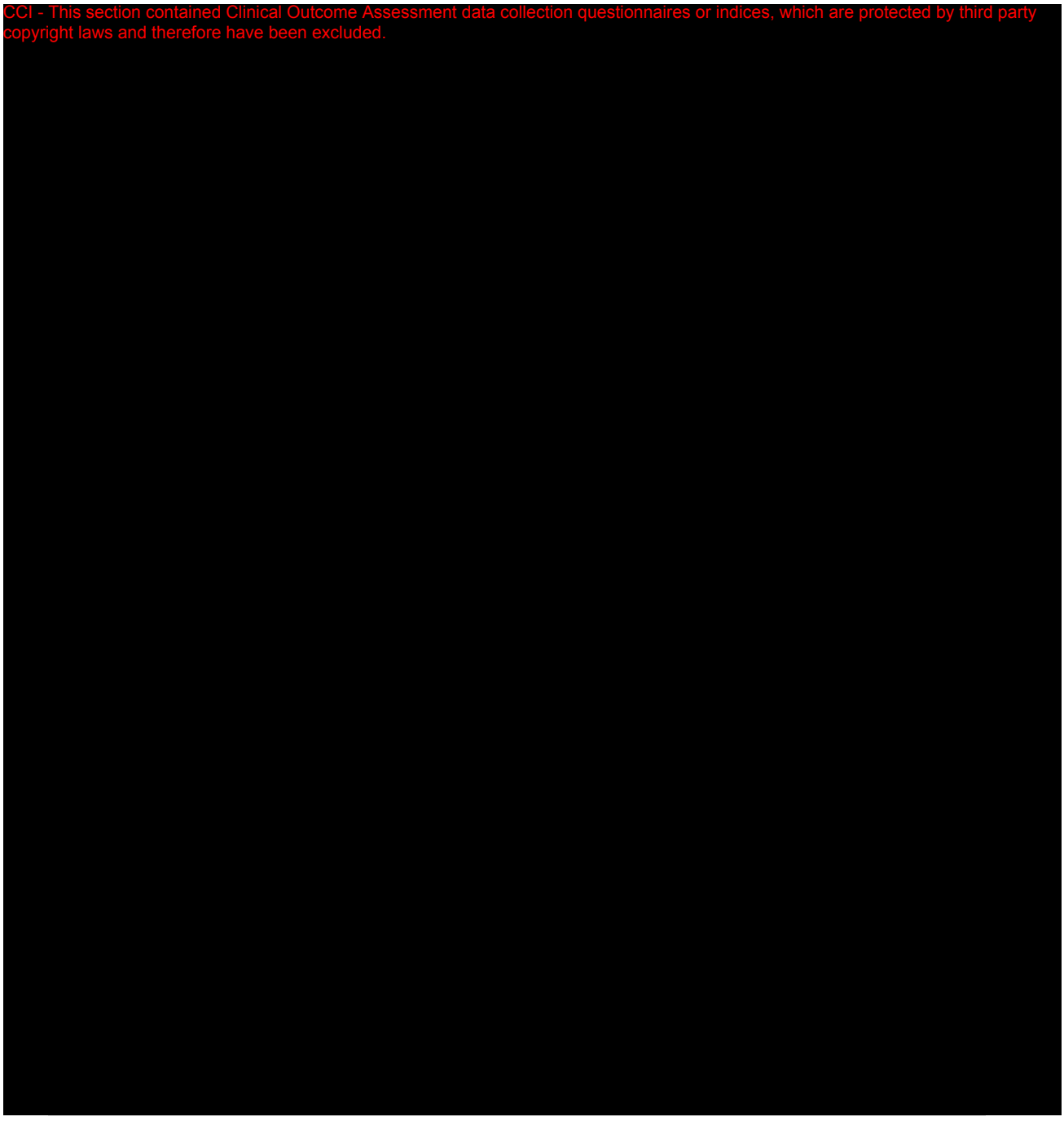
12.7. Appendix 7: Patient Reported Outcomes Questionnaires

12.7.1. FluPro

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

12.7.2. Katz ADL Score

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



12.8. Appendix 8 - Country Specific Requirements

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

12.9. Appendix 9 Statistical considerations

12.9.1. Introduction

This document describes the adaptive design for study 201023 for danirixin (DNX; GSK1325756) in hospitalized influenza subjects. The purpose of this document is to provide an overview of the trial design and simulation results. Simulations were performed using Dose finding module in FACTS version 4.0.

The trial design is based on the primary efficacy endpoint of time to clinical response. The goal of the trial is to assess the efficacy of DNX and to identify whether there is a dose with acceptable efficacy based on TTCR. An adaptive design is proposed that allows for dropping an in-effective dose, stopping the study for futility and/or stopping the study for early success.

The trial will enroll up to a maximum of approximately 300 subjects over the course of 3 flu seasons. Interim analyses will be conducted after each season with approximately 75 to 100 subjects. At each interim analysis, the predictive probability of success based on TTCR will be calculated and used to support go/no-go decisions.

12.9.2. Statistical Modeling

At each interim analysis and at the final analysis, the TTCR data will be analyzed with independent dose-response models. The adaptation will be based on the predictive probability of success.

12.9.2.1. Hazard Model:

Let T_0 be the time to clinical response for the control arm with exponential distribution

$$T_0 \sim Exp(\lambda)$$

Where λ is the hazard rate constant of subjects in the control arm, the parameter is modeled as:

$$\lambda \sim Gamma(n, \frac{n}{\mu})$$

Where n is prior weight parameter and μ is prior mean parameter, we set n=4 and μ=0.83 based on the hazard rate observed in study NAI114373.

And T_d be the time to clinical response for the dose level *d:*

$$T_d \sim Exp(h_d)$$

where $h_d = \lambda e^{\theta_d}$, and θ_d is log-hazard ratio.

12.9.2.2. The dose –response Model:

Independent dose-response model estimate the response for each arm separately with normal distribution.

$$\theta_d \sim N(\mu_d, v_d^2)$$

Where θ_d is log-hazard ratio compared to control arm on the treatment arm *d.* The two dose levels considered are d=1 (15 mg BID), and d=2 (50 mg BID). μ_d is the mean of dose d and v_d^2 is the variance of dose d. The same non-informative prior N(0,1) is used for all doses of the dose-response model.

12.9.3. Allocation

The allocation ratio is 1:2:2 for the control arm, DNX 15 mg (dose level 1) and DNX 50 mg (dose level 2), respectively. If an arm is dropped after interim analysis, allocation will be kept the same for the remaining arms and the study size will be decreased.

12.9.4. Evaluation of Arm Dropping, Trial Success and Futility

There will be one interim analysis after each season, with expectation that approximately 75-100 subjects will enroll in each season. Overall safety, biomarker and other efficacy data will be used for the decision of stopping the trial for futility and success. Early futility and success rules described below rely on the efficacy result based on TTCR.

12.9.5. Probability of success

Probability of success, denoted Prob(Success), will be used to evaluate futility, arm dropping and early success. Success is defined as a statistically significant treatment effect (p-value<0.025 for hazard ratio of TTCR >1) in a two-arm comparative superiority study with 300 subjects per arm, given observed data at interim and final analyses.

12.9.6. Arm Dropping

An ineffective DNX arm will be dropped if:

1. At least 75 subjects must have been enrolled.
2. Probability of success of the arm is less than 30%.

$$Prob_d(success) < 0.3$$

12.9.7. Early Futility

To stop early for futility two conditions are required:

1. At least 75 subjects must have been enrolled.
2. Probability of success of the best dose, denoted as $Prob_{max}(success)$, is less than 30%.

$$Prob_{max}(success) < 0.3$$

12.9.8. Early success

To stop early for success two conditions are required:

1. At least 75 subjects must have been enrolled.
2. Probability of success of the best dose, denoted as $Prob_{max}(success)$, is greater than 90%.

$$Prob_{max}(success) > 0.9$$

12.9.9. Trial completion

The final analysis will occur when both accrual and follow-up are complete for all subjects. If at the completion of the trial, $Prob_{max}(success)$ is at least 50% , there is evidence of efficacy with regard to TTCR.

$$Prob_{max}(success) > 0.5$$

12.9.10. Simulation Scenarios

In order to characterize and understand the performance of the design, we simulated the trial under several different scenarios.

Scenarios considered for the true hazard ratios for low dose and high dose DNX are shown in Table 11.

Table 11 Dose- Response profile for Hazard Ratio

	DNX 15mg + OSV	DNX 50mg + OSV
1. No effect	1	1
2. Small effect	1.2	1.2
3. Large effect	1.5	1.5
4. Mixed effect	1.2	1.5
5. High dose large effect	1	1.5

12.9.11. Operating Characteristics

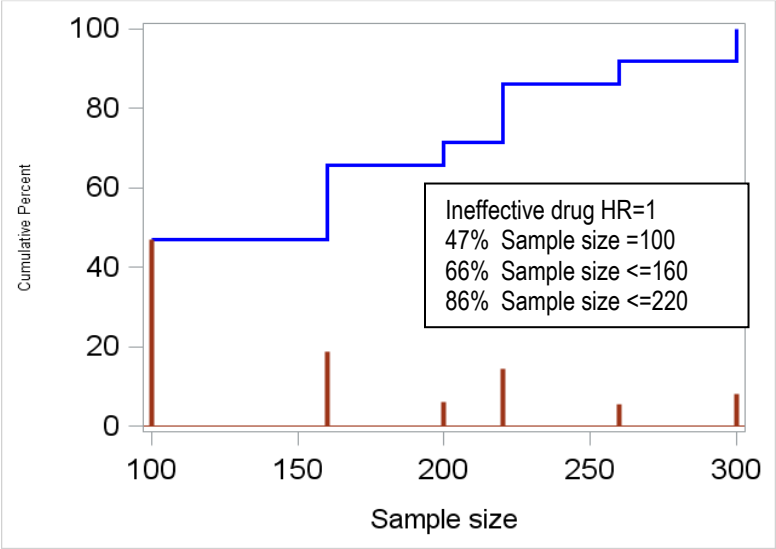
Table 12 shows the operating characteristics for different scenarios by interim analysis and final analysis. Figure 1 and Figure 2 show the possible sample size, corresponding probability of the sample size and cumulative probability of sample size under two selected scenarios.

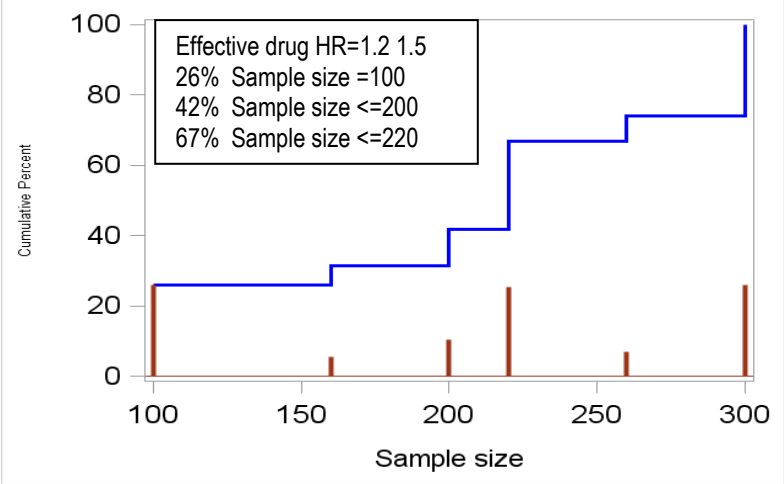
Table 12 Operating Characteristics by Interim of Selected Scenarios

Scenario	Hazard ratio	**Interim 1 n=100**				**Interim 2 n=200**				**Final**	
		P(drop low dose)	P(drop high dose)	P(stop study for futility) (Observed HR 0.85 – 1.2)	P(stop study for efficacy) (Observed HR 1.5 – 3.2)	P(drop low dose)	P(drop high dose)	P(stop study for futility) (Observed HR 1 – 1.15)	P(stop study for efficacy) (Observed HR 1.55 – 2.7)	Overall Power (Obs'd HR final success 1.27- 2)	Average Sample size
1. No effect	L: HR=1 H: HR=1	15%	19%	46%	1%	2%	3%	25%	0%	9%	**160**
2. Small effect	L: HR=1.2 H: HR=1.2	16%	15%	22%	5%	4%	5%	10%	3%	45%	208
3. Large effect	L: HR=1.5 H: HR=1.5	7%	8%	4%	26%	1%	1%	2%	19%	90%	208
4. Mixed effect	L: HR=1.2 H: HR=1.5	31%	2%	8%	18%	8%	0%	3%	13%	82%	207
5. High dose large effect	L: HR=1 H: HR=1.5	54%	1%	10%	18%	12%	0%	3%	12%	81%	191

Futility rule at Interim: Drop dose: Prob(success) for the dose < 30%, Stop study for futility: Prob(success) for best dose< 30%, Stop study for efficacy: Prob(success) for best dose> 90%; Final success criteria: Prob(success) for best dose>50%
Success is defined one side p<=0.025 in a two arm superiority study with n=300 per arm.

Figure 4 Sample Size Distribution for an effective drug and an ineffective drug





Location of brown line on x-axis shows possible study sample size, height of brown line shows probability of the sample size, and blue line shows the cumulative probability of study sample size. Top panel shows an example of an ineffective drug with HR =1 for both doses; the bottom panel shows an example of an effective drug with HR =1.2 for low dose and HR=1.5 for high dose.