Janssen Research & Development *

Clinical Protocol

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Pharmacokinetics, Safety, and Antiviral Activity of JNJ-63623872 in Combination With Oseltamivir in Adult and Elderly Hospitalized Patients With Influenza A Infection

Protocol 63623872FLZ2002; Phase 2
AMENDMENT 3

JNJ-63623872

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Protocol History 63623872FLZ2002			
Document Type and *File Name*	Issued Date	Amendment Type	Comments
Initial Clinical Trial Protocol *63623872FLZ2002_Protocol*	05-Aug-2015	-	-
Protocol Amendment I *63623872FLZ2002_Protocol_Amend_1*	23-Oct-2015	Substantial	For details, please refer to Section **Amendment 1**
Protocol Amendment II *63623872FLZ2002_Protocol_Amend_2*	09-Dec-2015	Substantial	For details, please refer to Section **Amendment 2**
Protocol Amendment III *63623872FLZ2002_Protocol_Amend_3*	This document	Substantial	For details, please refer to **Amendment 3**

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PROTOCOL AMENDMENTS

Amendment 3 (This document)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
Inconsistencies, corrections, and other edits within the protocol.

Rationale: Based on the conflict between Exclusion Criterion 8 and Section 10.2, Exclusion Criterion 8 was adapted to not allow subjects with chronic hepatitis C on treatment to enroll in the trial and the discontinuation criterion for hepatitis was removed from Section 10.2. In view of that, the discontinuation rules in Section 9.3.6 and Exclusion Criterion 7 were modified.

4.2 Exclusion Criteria
9.3.6 Specific Toxicities
10.2 Discontinuation of Study Treatment

Rationale: Toxicity management was updated to accommodate more severely ill patients in the hospital setting.

9.3.6 Specific Toxicities

Rationale: A second 300-mg tablet formulation containing the equivalent of JNJ-63623872 free base has been developed by the Sponsor. The formulation information was added to Section 14.1.

14.1 Physical Description of Study Drug(s)

Rationale: Exclusion Criterion 3 was modified to exclude severely immunocompromised subjects based on $CD4^+$ and absolute neutrophil counts. The discontinuation criterion for absolute neutrophil count was modified in Section 9.3.6.

SYNOPSIS
4.2 Exclusion Criteria
9.3.6 Specific Toxicities

Rationale: Based on FDA feedback, swabbing for local virology testing was adapted to be done from both nostrils instead of one (if feasible).

TIME AND EVENTS SCHEDULE – During Hospitalization (Up to discharge)
TIME AND EVENTS SCHEDULE – After discharge From Hospital
9.1.2 Screening Phase
9.4.1.2 Viral Kinetics (Nasal MT Swabs)

Rationale: Based on investigator feedback, timing of second dose was allowed to be brought forward with a maximum of 4 hours from scheduled dosing (previously protocol language only allowed for movement of dosing back 4 hours).

6 DOSAGE AND ADMINISTRATION

Rationale: Based on investigator feedback, a footnote was added to the Time and Events Schedule to allow a historical ECG (prior to ICF sign-off) to be used for screening/baseline, with a window of 1 day.

TIME AND EVENTS SCHEDULE – During Hospitalization (Up to discharge)
9.1.2 Screening Phase
9.3.3 Electrocardiogram

Rationale: Section 4.3 was updated following recent results of the oral contraceptive Phase 1 study (Study 63623872FLZ1009), which demonstrated no significant drug interaction between JNJ-63623872 and estrogen- and progesterone-based oral contraceptives.

1.1 Background
4.3 Prohibitions and Restrictions

Rationale: Based on results of the ^{14}C-ADME study (Study 63623872FLZ1007), there is little (~5%) CYP3A-mediated metabolism in vivo and therefore strong inhibitors or inducers of CYP3A metabolism were removed from the list of disallowed concomitant therapies.

8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: Clarification to Exclusion Criterion 12.

4.2 Exclusion Criteria

Rationale: Clarification to dose administration of oseltamivir based on the eGFR value.

SYNOPSIS
3.1 Overview of Study Design
6 DOSAGE AND ADMINISTRATION
9.1.3 Double-Blind Treatment Phase

Rationale: Clarifications and minor additions to Sections 11.5 and 11.6.

11.5 Safety Analyses
11.6 Efficacy Analyses

Rationale: Minor edits to below sections.

Front page
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1.3 Overall Rationale for the Study
3.1 Overview of Study Design
3.2 Study Design Rationale
14.2 Packaging

Amendment 2 (09 December 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
FDA feedback regarding (1) addition of a follow-up pregnancy test during treatment if pregnancy is a criterion for discontinuation of study drug and (2) addition of a hierarchal ordinal scale for clinical outcome as a secondary efficacy endpoint.

Rationale: Based on feedback by the FDA, a urine pregnancy test (for females of childbearing potential) was added to Day 5 procedures.

TIME AND EVENTS SCHEDULE
9.1.3 Double-Blind Treatment Phase
9.3.2 Clinical Laboratory Tests

Rationale: Based on feedback by the FDA, a hierarchal ordinal scale for clinical outcome was added as a secondary efficacy endpoint.

SYNOPSIS
2.1 Objectives
11.6 Efficacy Analyses

Based on feedback by the FDA, standard-of-care was added as additional therapy to hospitalized patients outside this protocol (at the investigator's discretion).

9.1.3 Double-Blind Treatment Phase

Rationale: Based on recommendations related to contraception and pregnancy testing in clinical trials published by the Clinical Trial Facilitation Group, the double-barrier method of contraception was removed.

4.3 Prohibitions and Restrictions

Rationale: Based on practical considerations, sparse PK sampling was adjusted for Day 2 and Days 4-7 to: "On Day 2 and Days 4-7: predose (≤1 hour prior to dosing) and between 1.5 and 6 hours after the morning or evening dose (whichever is the most convenient)."

TIME AND EVENTS SCHEDULE
9.2.1 Evaluations

Rationale: Based on practical considerations and to align with the current Investigator Brochure (no food effect), the requirement of dosing with food was removed.

SYNOPSIS
3.1 Overview of Study Design
6 DOSAGE AND ADMINISTRATION
9.2.1 Evaluations

Rationale: Level of consciousness was added to the vital sign measurement. The level of consciousness will be measured according to the AVPU scale (alert, voice, pain, unresponsive). The National Early Warning Score (NEWS) will be derived based on vital signs and AVPU scale at baseline and during hospitalization.

TIME AND EVENTS SCHEDULE
9.1.2 Screening Phase
9.3.4 Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure, blood oxygen saturation, level of consciousness)
11.5 Safety Analyses
REFERENCES

Rationale: Based on practical considerations, the limitation on regional recruitment was removed.

SYNOPSIS
3.1 Overview of Study Design
11.2 Sample Size Determination

Rationale: Minor edits were noted.

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Amendment 1 (23 October 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The FDA did not agree with the enrollment of adolescents because of insufficient Phase 2 safety and efficacy data in adults to support dosing in a pediatric population (Request for Additional Information 08 October 2015).

Rationale: Based on the request by the FDA, all text regarding inclusion of the adolescent population was removed. Accordingly, the sample size justification was re-written.

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Rationale: Re-wording was done to clarify exclusion criterion #3.

SYNOPSIS
4.2 Exclusion Criteria

Rationale: Minor errors were noted.

TIME AND EVENTS SCHEDULE

SYNOPSIS

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Pharmacokinetics, Safety, and Antiviral Activity of JNJ-63623872 in Combination With Oseltamivir in Adult and Elderly Hospitalized Patients With Influenza A Infection

JNJ-63623872 (previously known as VX-787) is a non-nucleotide inhibitor of the influenza A virus polymerase and is currently in Phase 2 development as treatment for influenza A infection.

Oseltamivir is an influenza neuraminidase inhibitor indicated for the treatment of acute, uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days and for prophylaxis of influenza in patients 1 year and older.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the pharmacokinetic (PK) parameters of JNJ-63623872 in combination with oseltamivir in elderly subjects (aged 65 to ≤85 years) compared to adults (aged 18 to ≤64 years) with influenza A infection.

Secondary Objectives

Secondary objectives include the assessment of the following parameters in the JNJ-63623872 treatment arm compared to the control arm:

1. Safety and tolerability.
2. The time to influenza viral negativity based on quantitative reverse transcription polymerase chain reaction (qRT-PCR) and/or viral culture from nasal mid-turbinate (MT) swabs and, if applicable, based on PCR-based rapid molecular testing from nasal MT swabs.
3. Viral load over time and rate of decline in viral load during treatment as measured by qRT-PCR and/or by viral culture.
4. Area under the curve (AUC) of viral load as measured by qRT-PCR and/or by viral culture.
5. Disease status and incidence of complications associated with influenza after the start of study treatment, and disease progression:
   - bacterial pneumonia (culture confirmed where possible),
   - other bacterial superinfections,
   - respiratory failure,
   - pulmonary disease (eg, asthma, chronic obstructive pulmonary disease [COPD]),
   - cardiovascular and cerebrovascular disease (eg, myocardial infarction, congestive heart failure [CHF], arrhythmia, stroke).
6. Change in duration and severity of clinical symptoms as measured by the Flu-PRO.
7. Time to improvement of vital signs.
8. Time to improvement of respiratory status.
9. Improvement on the ordinal scale.
10. Emergence of drug resistance as detected by genotype or phenotype.
11. Time to return to premorbid functional status.
12. Time to hospital discharge.

Exploratory Objectives

Exploratory objectives include the assessment of the following parameters in the JNJ-63623872 treatment arm compared to the control arm:

1. Use of antibiotics and/or corticosteroids during hospitalization.
2. Number of subjects admitted to the Intensive Care Unit (ICU).
3. Length of ICU stay for subjects transferred to the ICU after baseline.
4. Correlation between the decline in viral load (measured by qRT-PCR and/or viral culture) and changes in clinical symptoms.
5. PK/pharmacodynamic (PD) relationship (efficacy and safety).

Hypothesis

No formal hypothesis will be tested.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the effect of JNJ-63623872 600 mg twice daily (bid) versus (vs.) placebo, both in combination with oseltamivir 75 mg bid in adult and elderly hospitalized subjects with influenza A infection. Up to 90 subjects in total will be enrolled in this study. An effort will be made to enroll a minimum of approximately 24 subjects per age cohort.

Subjects who meet all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- JNJ-63623872 600 mg bid + oseltamivir 75 mg bid; OR
- JNJ-63623872 placebo bid + oseltamivir 75 mg bid

All study drugs will be taken orally.

The study will consist of a screening/baseline visit, a double-blind treatment period of 7 days, and a follow-up period of 21 days.

The entire study duration for each subject will be 28 days with study assessments daily during the treatment period, and on Days 10, 14, and 28 of the follow-up period. The study is considered complete with the completion of the last study assessment for the last subject participating in the study.

SUBJECT POPULATION

In order to start treatment as soon as possible after the start of the influenza infection, screening will occur on Day 1, before randomization and the first administration of study drug.

Key Inclusion Criteria

- Subject requires hospitalization to treat influenza infection and/or to treat complications of influenza infection.
- Subject tested positive for influenza A infection within 1 day of signing of the informed consent form (ICF) using a PCR-based rapid molecular diagnostic assay.
- Subjects must be capable of swallowing study medication tablets and capsules.
- Male or female subject, 18 to 85 years of age (extremes included).

Key Exclusion Criteria

- Subject received more than 3 doses of the influenza antiviral medication oseltamivir, zanamivir, or peramivir since the start of the influenza symptoms, or ribavirin within 6 months prior to screening.
- Subject is unwilling to undergo regular nasal MT swabs or has any physical abnormality which limits the ability to collect regular nasal specimens.
- Subject is known (considering lab results of the past 6 months) to be severely immunocompromised as defined by a CD4+ count <350 cells/mm3 or an absolute neutrophil count <750/mm3.
- Subject is undergoing peritoneal dialysis, hemodialysis, or hemofiltration.
- Subject has an estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m² according to the Modification of Diet in Renal Disease (MDRD) equation, assessed at screening or based on the most recent clinically relevant creatinine value if available.
- Subject has known moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C).

DOSAGE AND ADMINISTRATION

During the treatment period, all subjects will receive 1 of the following 2 dose regimens:

- JNJ-63623872 600 mg bid + oseltamivir 75 mg bid on Days 1 through 7; OR
- JNJ-63623872 placebo bid + oseltamivir 75 mg bid on Days 1 through 7.

Note: For subjects who receive only 1 dose on Day 1 (evening), dosing should continue until the morning of Day 8 so that all subjects receive 14 doses in total.

Oseltamivir dose should be reduced to 30 mg bid for subjects with an eGFR >30 and ≤60 mL/min/1.73 m² according to the MDRD equation. Dose can be adjusted from 30 mg to 75 mg and vice versa during the course of treatment based on the eGFR value.

All study drugs will be taken orally. All subjects will take 2 tablets (JNJ-63623872 or placebo) and 1 capsule (oseltamivir) bid.

PHARMACOKINETIC EVALUATIONS

All evaluations will be performed as specified in the Time and Events Schedule.

All subjects will undergo intensive PK sampling for the measurement of plasma concentrations of JNJ-63623872 on Day 3, at 8 different time points within the dosing interval. The first sample should be collected before (preferably immediately prior to) study drug intake (≤1 hour prior to the morning dose). Samples 2 to 8 should be collected at 1, 2, 4, 6, 8, 10, and 12 hours after the morning dose (and prior to the evening dose). For subjects who are discharged before Day 3, no intensive PK sampling will be performed.

All subjects will undergo sparse PK sampling for the measurement of plasma concentrations of JNJ-63623872 at the time points specified in the TIME AND EVENTS SCHEDULE.

Measurement of plasma concentrations of oseltamivir and oseltamivir carboxylate may be done at the sponsor's discretion.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

A population PK and PK/PD analysis of plasma concentration-time data of JNJ-63623872 will be performed using the nonlinear mixed-effects modeling approach.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity. The evaluations of safety and tolerability will include monitoring of adverse events (AEs) (including complications of influenza), clinical laboratory tests, electrocardiograms (ECGs), vital sign measurements, physical examinations, pregnancy testing, and assessment of specific toxicities at the time points specified in the TIME AND EVENTS SCHEDULE.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

EFFICACY EVALUATIONS

Patient-reported Outcomes

The impact of influenza infection and its treatment (safety and efficacy) on patient-reported symptoms and functioning will be evaluated at the time points specified in the TIME AND EVENTS SCHEDULE using Flu-iiQ^{TM} and Flu-PRO.

Viral Kinetics

Influenza viral titer will be determined and quantified in nasal MT swabs taken at the time points specified in the TIME AND EVENTS SCHEDULE.

RESISTANCE EVALUATIONS

Viral Sequencing

Nasal MT swabs collected will be used for sequence analysis of the polymerase basic protein 2 (PB2) region of the influenza virus polymerase and the neuraminidase gene at the time points specified in the TIME AND EVENTS SCHEDULE. Exploratory sequencing of other regions of the influenza virus genome may also be performed.

Phenotyping

Nasal MT swabs will be used for analysis of phenotypic resistance against JNJ-63623872 and other antivirals at the time points specified in the TIME AND EVENTS SCHEDULE.

BIOMARKER EVALUATIONS

Blood samples will be collected at the time points specified in the TIME AND EVENTS SCHEDULE for the exploration of blood biomarkers (eg, host ribonucleic acid [RNA], proteins including serum cytokines), on the premise that these markers may play a role in the blood concentrations, treatment response, or safety of JNJ-63623872 or oseltamivir, or the status and change of the influenza virus related disease. Where local regulations permit, an optional blood sample for exploratory host DNA research may also be collected.

In addition, nasal swabs collected for other testing may be used for biomarker analyses if available.

STATISTICAL METHODS

Since this is an exploratory study, no formal sample size calculation has been performed.

Up to 90 subjects in total will be enrolled in this study. An effort will be made to include at least 24 subjects for each cohort, with the total of subjects allowed to be recruited across both cohorts. It is anticipated that it is feasible to recruit at least 60 subjects, which would lead to an acceptable precision for the primary objective.

For age cohorts it was assumed that the number of hospitalizations would be about equal for elderly and non-elderly adults. In case 60 subjects are enrolled, there are 40 subjects on active treatment and it is assumed that at least 16 subjects are on active treatment in each cohort. For the comparison of PK

parameters of the cohort of elderly adults (test) vs. non-elderly adults (reference) with PK data in a 16 to 24 ratio and a between-subject coefficient of variation (CV) of 60%, the 90% confidence interval (CI) of the geometric mean ratio (GMR) for minimum plasma concentration (C_{min}) would be predicted to have a half-width of 35%, indicating that we can be 90% confident that the true GMR is in the interval observed GMR/1.35 to 1.35*GMR. If 90 subjects were enrolled with 60 on active treatment in a 24 to 36 ratio, the predicted half-width would be 28%.

For the safety objective of the study, the sample size of 40 to 60 subjects treated with JNJ-63623872 can be characterized by assessing the precisions for (potentially) observed treatment-emergent AEs. For example, if no related treatment-emergent serious adverse event (SAE) is observed in a sample of 60 subjects exposed to JNJ-63623872, it can be concluded with 95% confidence that the true incidence of related treatment-emergent SAEs will be less than 5%.

The primary PK analysis will be done on the PK-evaluable population, defined as all subjects who received active study treatment (JNJ-63623872 and oseltamivir), with evaluable PK measurements on Day 3.

Descriptive statistics will be used for all endpoints and will be tabulated by treatment arm and age cohort. No formal statistical hypothesis testing will be performed. Subgroup analyses may be summarized descriptively using baseline characteristics.

Primary Endpoint

- PK parameters of JNJ-63623872 (ie, C_{min}, C_{max}, and AUC_{12h}) established on Day 3.

Secondary Endpoints

1. The proportion of subjects experiencing AEs, SAEs, and treatment-emergent grade 1-4 laboratory abnormalities.
2. Time to return to usual activity and usual health (Questions 5 and 9 of the additional items for the Flu-PRO).
3. Time to significant reduction in influenza symptom severity.
4. Proportion of subjects with a significant reduction (to mild or none for all influenza symptoms) at each assessment.
5. Disease status and incidence of complications associated with influenza after the start of study treatment, and disease progression:
   - bacterial pneumonia (culture confirmed where possible),
   - other bacterial superinfections,
   - respiratory failure,
   - pulmonary disease (eg, COPD),
   - cardiovascular and cerebrovascular disease (eg, myocardial infarction, CHF, arrhythmia, stroke).
6. Duration and severity of clinical symptoms as measured by the Flu-PRO.
7. Time to improvement of vital signs.
8. Time to improvement of respiratory status.
9. Improvement on the ordinal scale.
10. Time to hospital discharge.
11. The time to influenza viral negativity based on qRT-PCR and/or viral culture from nasal MT swabs and, if applicable, based on PCR-based rapid molecular testing from nasal MT swabs.
12. Viral load over time and the rate of decline in viral load during treatment as measured by qRT-PCR and/or viral culture.

13. AUC of viral loads as measured by qRT-PCR and/or viral culture.
14. Resistance testing will be performed on all baseline samples as well as on qRT-PCR-positive post-baseline samples. Genotypic assays (sequencing of full length PB2 and other gene segments if applicable) will be used to determine resistance against JNJ-63623872. Phenotyping may be done at the sponsor's discretion. Resistance testing for neuraminidase inhibitors will also be performed as applicable.

Exploratory Endpoints

1. Length of ICU stay for subjects transferred to the ICU after baseline will be collected.
2. Use of antibiotics and/or corticosteroids during hospitalization.
3. Number of subjects admitted to the ICU.
4. Correlation between the decline in viral load (measured by qRT-PCR and/or viral culture) and changes in clinical symptoms.
5. PK/pharmacodynamic (PD) relationship (efficacy and safety).

An independent data monitoring committee (IDMC) will be established to monitor safety and efficacy data on a regular basis.

An interim analysis may be performed to support regulatory activities.

Pharmacokinetic Analyses

Descriptive statistics will be calculated for plasma concentrations of JNJ-63623872 at each sampling time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation (SD), %CV, geometric mean, median, minimum, and maximum.

For each subject treated with JNJ-63623872, JNJ-63623872 plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis in order to get a general overview.

Statistical analysis will be performed for the PK-evaluable population. Elderly adults (65 to ≤85 years) will be compared to non-elderly adults (reference) to investigate the relative effect of age. The primary PK parameters are C_{max}, C_{min}, and AUC_{12h}. AUC_{12h} will be omitted as primary parameter for an age cohort if more than half of the subjects of that age cohort do not have a reliable value.

Special attention will be paid to the plasma concentrations and PK parameters of those subjects who have discontinued the study for an AE, or who experienced an AE of at least grade 3, or an SAE.

Oseltamivir and oseltamivir carboxylate may be analyzed at the sponsor's discretion.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of JNJ-63623872 exposure (AUC_{12h}, C_{max}, or C_{min}) with efficacy (ie, change in viral load from baseline and virologic response) and safety (including AEs and laboratory abnormalities) will be explored. Other exploratory analyses may be performed (eg, AUC of viral load).

Safety Analyses

All safety endpoints will be evaluated on the Safety population, consisting of all subjects who received at least one dose of study drug and will be analyzed by drug received. Safety will be evaluated by means of AEs (including influenza complications), clinical laboratory tests, ECGs, vital signs, physical examinations, pregnancy testing, and specific toxicities. The safety analysis will be done using descriptive statistics for the Safety population and for each study phase separately (treatment, follow-up, and the combination of both).

Efficacy Analyses

The efficacy endpoints will be analyzed on the Full Analysis Set, consisting of all subjects who were randomized, treated and had a confirmed influenza A infection, and will be analyzed by drug received. Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and by age cohort. For comparisons on defined endpoints of active vs. control treatment, appropriate pre-specified statistical analyses will be performed estimating the treatment difference including the associated 95% CI.

Biomarker Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between study subjects. Analyses may be conducted at the sponsor's discretion and reported separately from this study.

TIME AND EVENTS SCHEDULE – DURING HOSPITALIZATION (UP TO DISCHARGE)

Phase	Screening		Treatment						Follow-up		
Day	1[a]		2	3	4	5	6	7	10	14	28
	Screening / Baseline[b]	Treatment[c]									Safety Follow-up Visit / Final Study Visit[d]
Screening/Administrative											
ICF	X										
Inclusion/exclusion criteria	X[e]										
Medical history, demographics	X										
Physical exam	X										X
Symptom-directed physical exam			Daily until discharge or until Day 14 (whichever comes first)								
Height and weight[f]	X										
12-lead ECG	X[w]			X[g]							X
Urine pregnancy test (female subjects of childbearing potential)	X					X					X
Study Drug Administration											
Randomization	X										
Administration of study drug (bid)		X[h]	X	X	X	X	X	X[h]			
Virology Assessments											
Nasal MT swab[i] for local PCR-based rapid molecular testing	X[k,l]		The day before and/or the day of discharge from the hospital[k,m]								
Nasal MT swab[j] for central testing	X[k]		Daily until discharge or until Day 14 (whichever comes first)[k]								
Efficacy/Safety Assessments											
Vital signs/pulse oximetry[v]	X		3X daily until discharge or until Day 14 (whichever comes first)[n]								X
Influenza symptoms and impact (Flu-iiQ™)[o]	X		X	X	X	X	X	X	X	X	X
Influenza symptoms (Flu-PRO)[p]	X		X	X	X	X	X	X	X	X	X
Hematology, chemistry, coagulation, serology	X[q]			X[r]		X[r]			X[r]		X[r]
Urinalysis	X			X		X			X		X
Pharmacokinetics	X[k,s]		X[k,s]	X[k,t]	X[k,s]	X[k,s]	X[k,s]	X[k,s]			
Blood biomarkers (proteins)	X		X	X	X	X		X	X		X
Blood biomarkers (mRNA)	X		X		X			X			X
Biomarkers (DNA)[u]	X										
Adverse events (including complications of influenza)	X		X	X	X	X	X	X	X	X	X
Concomitant medication											
Recording	X		X	X	X	X	X	X	X	X	X

[a] Day 1 encompasses signing of the informed consent form (ICF) approximately + 24 hours, and can be split over 2 calendar days if needed.

[b] All screening and baseline procedures should take place prior to the first study drug intake.

[c] Depending on the time of hospital admission and the timing of screening/baseline assessments, eligibility may only be established on the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility.

[d] Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a safety follow-up visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional safety follow-up visit.

[e] Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation.

[f] Height and body weight are only to be measured at screening if not already available in the subject's chart and if practically feasible.

[g] Electrocardiogram (ECG) to be performed approximately 4 hours after the morning dose.

[h] Depending on the time of screening/enrollment, subjects will receive 1 dose (evening) or 2 doses (morning and evening) of study drug on Day 1. For subjects who receive only 1 dose on Day 1 (evening), dosing should continue until the morning of Day 8 so that all subjects receive 14 doses in total.

[i] Local virology testing: Nasal mid-turbinate (MT) swabs should be obtained from the left and the right nostrils (from both nostrils if feasible, but from only one nostril otherwise) and pooled into the same collection tube. Sampling should be done at approximately the same time when required. Sampling should be done according to the local testing requirements.

[j] Central virology testing: Nasal mid-turbinate (MT) swabs should be obtained from the left and the right nostrils and pooled into the same collection tube. Sampling should be done at approximately the same time each day throughout the study.

[k] At the time points where both nasal MT swabs and pharmacokinetic (PK) samples are obtained, these samples should be obtained as close together in time as possible.

[l] An earlier sample within 1 day before signing of the ICF can be used in lieu of the baseline nasal swab requirement.

[m] Assessment to be performed on the day of discharge from the hospital and, if possible, the day before.

[n] Vital signs are to be measured 3 times daily: in the morning (prior to study drug intake if applicable), approximately half-way in the middle of the day, and in the evening (prior to study drug intake if applicable).

[o] The Flu-iiQ™ (and additional daily diary items) will be completed twice daily (preferably in the morning and in the evening) on Days 1 through 14 and once daily (preferably in the evening) on Days 15 through the Final Study Visit/Safety Follow-up Visit.

[p] The Flu-PRO (and additional daily diary items) will be completed once daily (preferably in the evening) throughout the study.

[q] Hepatitis A, B, and C serology testing will be done at screening for all subjects. Follicle-stimulating hormone (FSH) will be tested at screening for female subjects who are amenorrheic for 12 months or less.

[r] If feasible, safety blood samples will be collected after fasting for at least 10 hours.

[s] Sparse PK sampling will be performed as follows (for as long as subjects are hospitalized):

- on Day 1: predose (≤1 hour prior to study drug intake), between 1.5 and 6 hours, and 12 hours after that same study drug intake (and prior to the next study drug intake). For subjects who start dosing in the morning of Day 1, a trough sample will be taken predose on Day 2 (≤1 hour prior to the morning dose).
- on Day 2 and Days 4-7: predose (≤1 hour prior to dosing) and between 1.5 and 6 hours after the morning or evening dose (whichever is the most convenient).

[t] Intensive PK sampling will be performed over 12 hours: predose (≤1 hour prior to the morning dose) and 1, 2, 4, 6, 8, 10, and 12 hours after the morning dose (and prior to the evening dose). ***Note:*** For subjects who are discharged before or on Day 3, no intensive PK sampling will be performed.

[u] The pharmacogenomic (DNA) blood sample is optional and will preferably be collected at the baseline visit. However, if necessary eg, in case of a technical failure, it may be collected at a later time point without constituting a protocol deviation.

[v] Vital signs/pulse oximetry includes also assessment of level of consciousness (AVPU: alert, voice, pain, unresponsive).

[w] A historical ECG within 1 day before signing of the ICF can be used in lieu of the baseline ECG requirement.

TIME AND EVENTS SCHEDULE – AFTER DISCHARGE FROM HOSPITAL

Note: This Time and Events Schedule should start with the Study Day number following the day of discharge from the hospital (for example: subjects discharged on Study Day 9 would start with Day 10 procedures on this schedule). When subjects are discharged, the remainder of the study visits should be carried out as outpatient visits (preferably on-site or, if not feasible, at the subject's home) or by telephone follow-up as indicated in the flowchart below. Every effort should be made to perform all of the assessments as outlined below (either on-site or at the subject's home), if practically feasible. In case of readmission to the hospital, subjects will continue to follow this Time and Events Schedule until the end of the study.

Phase	**Treatment[a]**			**Follow-up**			
Day	**2/3/4[b]**	**5 +/-1 Day**	**6/7[b]**	**8[c] +/-1 Day**	**10 +/-1 Day**	**14 +/-2 Days**	**28 +/-3 Days**
	Phone Follow-up	**On-site/At home**	**Phone Follow-up**	**On-site/At home**	**On-site/At home**	**On-site/At home**	**Safety Follow-up Visit / Final Study Visit[d] On-site**
Study Drug Administration							
Administration of study drug (bid)[a]	X	X	X				
Virology Assessments							
Nasal MT self-swab[e] for local PCR-based rapid molecular testing	Daily on days with no outpatient visit						
Nasal MT swab for local PCR-based rapid molecular testing[e]		X[g]		X[g]			
Nasal MT swab for central testing[f]		X[g]		X[g]	X	X	
Efficacy/Safety Assessments							
Vital signs/pulse oximetry		X			X		X
Physical exam							X
Symptom-directed physical exam		X			X		
12-lead ECG							X
Urine pregnancy test (female subjects of childbearing potential)		X					X
Influenza symptoms and impact (Flu-iiQ™)[h]	X	X	X	X	X	X	X
Influenza symptoms (Flu-PRO)[i]	X	X	X	X	X	X	X
Hematology, Chemistry, Coagulation		X[j]			X[j]		X[j]
Urinalysis		X			X		X
Pharmacokinetics		X[g,k]		X[g,k]			
Blood biomarkers (proteins and mRNA)[l]		X		X			X
Adverse events (including complications of influenza)	X	X	X	X	X	X	X

Phase	Treatment[a]			Follow-up			
Day	**2/3/4[b]**	**5 +/-1 Day**	**6/7[b]**	**8[c] +/-1 Day**	**10 +/-1 Day**	**14 +/-2 Days**	**28 +/-3 Days**
	Phone Follow-up	**On-site/At home**	**Phone Follow-up**	**On-site/At home**	**On-site/At home**	**On-site/At home**	**Safety Follow-up Visit / Final Study Visit[d] On-site**
Concomitant medication							
Recording	X	X	X	X	X	X	X

[a] If the subject is discharged while on study treatment, he/she will receive study medication for at-home use.
[b] Subjects do not need to be seen on these days. A telephone contact is recommended to ensure compliance with study drug intake.
[c] For subjects who receive only 1 dose on Day 1 (evening), dosing should continue until the morning of Day 8 so that all subjects receive 14 doses in total.
[d] Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the study site for a safety follow-up visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional safety follow-up visit.
[e] Local virology testing: Nasal MT self-swabbing and swabbing by site staff should only continue for subjects for which the last sample before discharge was positive. Self-swabbing and swabbing by site staff should be continued until the subject is confirmed influenza negative or until Day 10 at the latest. Subjects will be instructed on how to self-swab at home and how to store the nasal samples at home until their next outpatient study visit. Nasal MT (self-)swabs should be obtained from the left and the right nostrils (from both nostrils if feasible, but from only one nostril otherwise) and pooled into the same collection tube. Sampling should be done at approximately the same time when required. Sampling should be done according to the local testing requirements.
[f] Central virology testing: Nasal MTswabs should be obtained from the left and the right nostrils and pooled into the same collection tube. Sampling should be done at approximately the same time when required. Nasal MT swabs for central testing should be continued for all subjects, at the indicated time points.
[g] At the time points where both nasal MT swabs and PK samples are obtained, these samples should be obtained as close together in time as possible.
[h] The Flu-iiQ™ (and additional daily diary items) will be completed twice daily (preferably in the morning and in the evening) on Days 1 through 14 and once daily (preferably in the evening) on Days 15 through the Final Study Visit/Safety Follow-up Visit.
[i] The Flu-PRO (and additional daily diary items) will be completed once daily (preferably in the evening) throughout the study.
[j] If feasible, safety blood samples will be collected after fasting for at least 10 hours.
[k] Sparse PK sampling will be performed as follows (if practically feasible):

- on Day 5: at any time during the visit.
- on Day 8: at any time during the visit.

[l] Two blood samples will be taken.

ABBREVIATIONS

AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASMP	Anticipated Events Safety Monitoring Plan
AST	aspartate aminotransferase
AUC_{th}	area under the plasma concentration-time curve from time 0 to t hours after dosing
AVPU	alert, voice, pain, unresponsive
bid	bis in die; twice daily
BMI	body mass index
BUN	blood urea nitrogen
C_{0h}	predose plasma concentration
CDC	Centers of Disease Control and Prevention
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COPD	chronic obstructive pulmonary disease
CPAP	clinical pharmacology analysis plan
CPK	creatine phosphokinase
C_{trough}	plasma concentration just prior to the beginning or at the end of a dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	Electronic Data Capture
EENT	eyes/ears/nose/throat
eGFR	estimated glomerular filtration rate
(e)PRO	(electronic) patient reported outcome
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GMR	geometric mean ratio
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	International Review Board
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
LS	least square
MCH	mean corpuscular hemoglobin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

MT	Mid-turbinate
NEWS	National Early Warning Score
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptide
PB2	polymerase basic protein 2
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	product quality complaint
PT	prothrombin time
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's correction
QTcF	QT interval corrected for heart rate according to Fridericia's correction
QTcL	QT correction derived by linear regression
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time to reach C_{max}
UGT	uridine diphosphate-glucuronosyltransferases
USP	United States Pharmacopeia
vs.	versus
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

JNJ-63623872 (formerly known as VX-787) is a non-nucleotide inhibitor of the polymerase basic protein 2 (PB2) subunit of the influenza A virus polymerase complex and is currently in Phase 2 development as treatment for influenza A infection.

For the most comprehensive nonclinical and clinical information regarding JNJ-63623872, refer to the latest version of the Investigator's Brochure for JNJ-63623872.[6] Please consult the manufacturer's prescribing information for oseltamivir (Tamiflu®) for full safety information.[14,15]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Both seasonal and pandemic influenza are a significant cause of morbidity and mortality worldwide. For example, the 2009 H1N1 influenza pandemic in the United States was responsible for an estimated 60.8 million cases, 274,000 hospitalizations, and over 12,400 deaths.[9] Because the efficacy of the current annual hemagglutinin-based or modified live influenza virus vaccines depends on accurately predicting the viral strains prior to each influenza season or pandemic, there exists an unmet need for new antiviral agents that are broadly effective.[1]

As well as ongoing vaccine development, several antiviral drugs have been developed for influenza. These drugs have been shown to shorten the duration and reduce the severity of symptoms if taken early after the onset of symptoms (within 24 to 48 hours). They can also be taken as prophylaxis against infection. The 2 main classes of antiviral drugs used against influenza are the neuraminidase inhibitors, such as oseltamivir (Tamiflu), peramivir (Rapivab™), and zanamivir (Relenza®), and the viral M2 protein inhibitors, such as amantidine (Symmetrel®) and rimantadine (Flumadine®). Unfortunately, influenza strains have emerged that show resistance to both of these classes of drugs. In addition, these drugs have limitations in that they need to be administered no later than 24 to 48 hours after infection, and therefore many patients are not eligible for therapy when they present for treatment.

A desired profile of a novel influenza antiviral includes: (1) rapid onset of protective effects leading to an expanded treatment window; (2) better activity in patients with high viral load; (3) inhibition of both production and release of virus; (4) maintenance of potency against neuraminidase- and M2-inhibitor-resistant viral strains; (5) safe and well tolerated. JNJ-63623872, an inhibitor of the viral replication complex, potentially meets all of these criteria.

Nonclinical Studies

JNJ-63623872 hemihydrate has a molecular formula of $C_{20}H_{19}F_2N_5O_2$•HCl•0.5 H_2O and a molecular weight of 399.39 Da.

Nonclinical Pharmacology

JNJ-63623872 is a non-nucleotide inhibitor of the PB2 subunit of the influenza A virus polymerase complex. JNJ-63623872 is a potent inhibitor of influenza A virus replication in vitro: using cytopathic effect-based methods in Madin-Darby canine kidney cells, the mean 50% effective concentration (EC_{50}) of JNJ-63623872 was 1.1 nM for a panel of 36 influenza A strains, including contemporary and historical H1N1 strains, including 2009 pandemic strains, H3N2 strains, and the highly pathogenic H5N1 strain and H7N9 strains, as well as strains that were resistant to neuraminidase inhibitors. Little or no antiviral activity was seen against influenza B strains. JNJ-63623872 was also effective at inhibiting viral replication in ribonucleic acid (RNA) based assays and in experiments using normal human bronchial epithelial cells. Inhibition of viral replication was observed even when JNJ-63623872 was added after the initiation of viral infection, and the magnitude of viral replication inhibition was largely independent of multiplicity of infection.

In vitro synergy/antagonism experiments show synergy of JNJ-63623872 with the neuraminidase inhibitors oseltamivir and zanamivir, and additivity to synergy with favipiravir (an investigational nucleoside inhibitor).

In a murine model of pulmonary influenza infection, prophylactic treatment with JNJ-63623872 administered at 3 or 10 mg/kg twice daily (bid) provided protection from influenza-induced mortality and morbidity; including when the start-to-treat window for JNJ-63623872 was delayed as long as 96 hours after influenza infection. JNJ-63623872 (up to 30 mg/kg) decreased lung viral titers (up to 1.8 $\log_{10}$ reduction) when administered to mice 24 hours after influenza A virus infection, and pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested that the minimum plasma concentration (C_{min}) was the PK parameter driving JNJ-63623872 antiviral activity. The predicted minimally efficacious therapeutic exposure assuming a 96-hour start-to-treat window was an area under the plasma concentration-time curve from time 0 to 24 hours after dosing (AUC_{24h}) of approximately 3,000 ng.h/mL, with an estimated C_{min} of 30 ng/mL; based on improved efficacy at exposures associated with 10 mg/kg regimens in the mouse model, 100 ng/mL is targeted as the therapeutic C_{min}.

Nonclinical Pharmacokinetics

In vitro studies indicate that JNJ-63623872 is highly permeable, subject to P-glycoprotein (P-gp) transport, and is not an inhibitor of P-gp in vitro at 0.1 to 100 µM. JNJ-63623872 oral bioavailability was high in mice and rats, moderate in dogs, and low in monkeys.

JNJ-63623872 plasma protein binding ranged from 98% to >99.9% across species, and was concentration independent over a range of 1 to 10 µM. JNJ-63623872 was distributed widely throughout the body with the exception of the brain. There was no apparent melanin binding in pigmented skin or eyes.

JNJ-63623872 was metabolized in rat, dog, monkey, and human hepatocytes, and the metabolites detected in monkey cells were the most similar to those detected in human cells. JNJ-63623872 elimination was governed by both Phase I cytochrome P450 (CYP) enzymes (namely CYP3A4)

and aldehyde oxidase, as well as Phase II glucuronidation via uridine diphosphate-glucuronosyltransferases (UGT) 1A3 and 1A9. The primary biotransformation pathways of JNJ-63623872 in rats are glucuronidation and oxidation. Based on in vitro results from CYP enzyme induction and inhibition studies, the potential for drug-drug interactions is expected to be low.

The estimated systemic clearance following intravenous (IV) administration of JNJ-63623872 was approximately 51%, 44%, and 26% of hepatic blood flow in rats, dogs, and monkeys, respectively, with an elimination half-life ranging from 2.7 to 21 hours.

After oral administration of ^{14}C-JNJ-63623872 to bile duct cannulated Sprague Dawley male rats, means of 79.1%, 13.7%, and 0.529% of the administered radioactivity were excreted in bile, feces, and urine, respectively, through 168 hours postdose.

JNJ-63623872 was found to inhibit organic anion transporting polypeptide (OATP) 1B1 with a 50% inhibitory concentration (IC_{50}) of 0.6 μM. JNJ-63623872 was also determined to be a substrate of OATP1B1.

Toxicology

No genotoxicity (mutagenicity, in vitro chromosomal aberration, or mammalian erythrocyte), phototoxicity (in vitro), safety pharmacology (battery of in vitro studies designed to evaluate effects of JNJ-63623872 against multiple cellular targets and a battery of in vivo cardiovascular, central nervous system, and respiratory systems), or reproductive (embryo-fetal, fertility, and early embryonic development) liabilities have been identified for JNJ-63623872. There were no toxicological effects in acute studies in mice and rats at doses up to 1,000 mg/kg. In studies where rats and monkeys were administered JNJ-63623872 at very high doses for 14 days, specific organ toxicity (liver, kidney, bone marrow, spleen, lymph nodes) and other toxicological findings were noted at doses of 250 mg/kg/day and above. The no observed adverse effect level (NOAEL) in 14-day, repeat-dose toxicology studies was 100 mg/kg/day in rats and 150 mg/kg/day in monkeys. These doses correspond to animal to human exposure multiples (AUC_{0-24h} basis) of 40-fold and 24-fold in male and female rats, respectively, and 2-fold and 4-fold in male and female monkeys, respectively, based on a clinical dose of 600 mg JNJ-63623872 bid for 5 days.

Clinical Studies

At the time of protocol writing, data were available from 4 completed clinical studies: three Phase 1 studies and one Phase 2a challenge study.

Human Pharmacokinetics

Food has a modest effect on bioavailability. When JNJ-63623872 was administered as either capsule or tablet with a high-fat meal, the AUC from time of dosing extrapolated to infinity ($ACU_{0-\infty}$) was similar compared to fasted conditions. However, the maximum plasma concentration (C_{max}) was decreased by 9% for the capsule formulation and increased by 53% for the tablet formulation. The absolute bioavailability of the tablet is approximately 46%.

Following IV administration, the mean estimated volume of distribution at steady-state is 407 L, much larger than typical blood volume, suggesting JNJ-63623872 is extensively distributed.

Exploratory metabolite profiling suggested that JNJ-63623872 was the major component circulating in the plasma and only 1 glucuronide metabolite (<5%) was identified at steady-state.

Renal elimination of unchanged JNJ-63623872 is <1% following single oral doses.

Following single ascending doses of JNJ-63623872 capsules administered orally in the fasted state to healthy subjects, exposure (AUC) was slightly greater than dose proportional from 200 mg to 800 mg, less than dose proportional from 800 mg to 1,200 mg, and slightly greater than dose proportional from 1,200 mg to 1,600 mg (study VX11-787-001) (Table 1). JNJ-63623872 plasma concentrations exhibit bi-phasic kinetics, eliminated initially at a more rapid rate, followed by a slower terminal elimination phase. The mean terminal elimination half-life ($t_{1/2term}$) ranges from approximately 13 to 28 hours following single doses of JNJ-63623872.

Following a single 100 mg IV dose infused over 60 minutes, plasma concentrations of JNJ-63623872 declined more rapidly followed by a slower terminal elimination phase. The mean $t_{1/2term}$ was 20 hours, similar to oral doses.

Table 1: Selected Single Dose JNJ-63623872 Pharmacokinetic Parameters

					Mean (CV%)		
Study	Dose (mg)	Formulation Fasted/Fed	N[a,b]	t_{max}[c] (h)	C_{max} (ng/mL)	AUC_{∞} (ng.h/mL)	$t_{1/2term}$ (h)
001	200	Capsule Fasted	6	1.25 (1.00, 2.00)	229 (49.6)	2,080 (50.9)	14.0 (32.3)
	400	Capsule Fasted	6	3.00 (1.00, 4.00)	602 (35.8)	5,690 (31.1)	12.9 (18.2)
	800	Capsule Fasted	6	1.50 (1.00, 6.00)	1,120 (61.8)	12,700 (41.2)	22.3 (26.9)
	1,200	Capsule Fasted	6	2.50 (1.00, 4.00)	1,580 (98.1)	12,500 (34.5)	17.1 (35.3)
	1,600	Capsule Fasted	6	2.50 (1.00, 6.00)	2,030 (83.2)	21,800 (42.8)	27.8 (60.9)
002	600	Capsule Fasted	18	2.00 (1.00, 6.00)	558 (57.7)	7,856 (59.0)	20.9 (60.2)
	600	Tablet Fasted	18	3.00 (1.00, 6.00)	909 (45.2)	9,809 (50.5)	20.8 (78.2)
	600	Tablet Fed	18	2.00 (1.00, 12.00)	1,480 (71.2)	8,968 (42.8)	19.4 (16.1)
	100	IV 60-minute infusion	8	0.75 (0.50, 1.00)	1,910 (15.3)	3,580 (56.6)	20.8 (63.8)

Source: studies VX11-787-001 and VX12-787-002
[a] AUC_{∞} not reported for all subjects due to AUC_{extrap} >25%
[b] terminal elimination half-life ($t_{1/2term}$) not reported for all subjects due to $t_{1/2}$ exceeding last sample collection
[c] median (range)

The mean accumulation index for AUC ranged from 1.6 to 2.5 following once daily doses of 100 mg, 400 mg, and 800 mg for 10 days. There are no apparent time-dependency characteristics with repeat dosing. Steady-state is generally achieved after 3 days of dosing. Pharmacokinetic

parameters observed in healthy subjects appear to be similar with or without prior inoculation of influenza A virus in a virus challenge model.

Clinical Efficacy

VX11-787-101 was a Phase 2a challenge study with a randomized, double-blind, placebo-controlled design. Four dose regimens of JNJ-63623872 or placebo were administered orally at 24 hours after viral inoculation and continued for 5 consecutive days: 100 mg once daily, 400 mg once daily, and single 900 mg or 1,200 mg loading dose followed by 600 mg once daily for 5 days (capsule). A total of 106 healthy subjects were enrolled and inoculated, 104 subjects received study drug (n=72 JNJ-63623872; n=32 placebo).

Healthy subjects were inoculated intranasally with 1.0 mL of a 50% tissue culture infective dose of 5.0 to 5.5 $\log_{10}$/mL live influenza A/Wisconsin/67/2005 (H3N2) challenge strain virus on Day 0.

Results showed that JNJ-63623872 was effective in decreasing viral shedding in subjects with an active influenza A infection, with a concomitant reduction in symptoms.

- A statistically significant dose response trend was observed on the AUC of viral shedding by tissue culture assay (p=0.036) and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) (p=0.031).
- The 1,200/600-mg treatment group had a statistically significant reduction of the AUC of viral shedding by tissue culture (p=0.010) and by qRT-PCR (p=0.014) compared with placebo.
- The 1,200/600-mg treatment group had a statistically significant reduction of the AUC (p=0.040), peak (p=0.034), and duration (p<0.001) of patient-reported influenza-like symptom scores compared with placebo.
- The 1,200/600-mg treatment group had a statistically significant decrease in the duration (p=0.001) of patient-reported composite clinical symptom score compared with placebo.

These results suggest that JNJ-63623872 has the potential to be a novel treatment for patients with influenza A infection.

Clinical Virology

Population sequence analyses of the PB2 segment in subjects in study VX11-787-101 (healthy subjects challenged with influenza virus on Day 0, and treated with JNJ-63623872 for Days 1 through 5) identified a variant (PB2 M431I) that was observed in multiple subjects (n=4). This amino acid change confers a 57-fold decrease in sensitivity to JNJ-63623872 in in vitro studies but the virus had reduced replication capacity compared to wild type strains.

Additional variants at 3 PB2 positions that had previously been associated with mutations that cause a decrease in sensitivity to JNJ-63623872 in vitro (S324C, K376R, and M431L/R/V) were also observed in single JNJ-63623872 treated subjects.

Clinical Safety

JNJ-63623872 has been studied in single oral doses (studies VX11-787-001 and VX12-787-002), multiple oral doses (studies VX11-787-001 and VX-787FLZ1001), multiple oral doses coadministered with oseltamivir (study 63623872FLZ1001), and single IV doses (study VX12-787-002) in healthy subjects. In addition, JNJ-63623872 has been studied in multiple oral doses in subjects infected with a challenge dose of influenza A (study VX11-787-101). JNJ-63623872 was generally safe and well tolerated. There were no serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation of study drug.

Safety in Phase 1 studies: In healthy subjects receiving single oral doses of JNJ-63623872 up to 1,600 mg once daily, multiple oral doses of JNJ-63623872 up to 800 mg once daily for 10 days, and multiple oral doses up to 600 mg bid for 10 days, all AEs were mild in severity, except for a single case of moderate syncope (study VX12-787-002), and a single case of moderate diarrhea (study VX-787FLZ1001). The most frequently occurring AEs in healthy subjects administered single doses of JNJ-63623872 or placebo were headache (7.9% JNJ-63623872, 7.1% placebo) and diarrhea (6.6% JNJ-63623872, 7.1% placebo). The most frequently occurring AEs after multiple doses of JNJ-63623872 up to 800 mg once daily were also headache (11.1% JNJ-63623872, 16.7% placebo) and diarrhea (11.1% JNJ-63623872, 0% placebo), as well as somnolence (11.1% JNJ-63623872, 0% placebo). The most frequently occurring AEs after multiple doses of JNJ-63623872 up to 600 mg bid for 10 days were gastrointestinal disorders, specifically diarrhea (58.3% JNJ-63623872, 0% placebo).

There were no AEs in healthy subjects receiving single IV doses of 100 mg JNJ-63623872 via a solution of 2 mg/mL JNJ-63623872.

Oral hormonal contraceptive is acceptable as a highly effective user-dependent contraceptive method (63623872FLZ1009).

Safety in Phase 2 studies: In 72 healthy subjects inoculated with a challenge dose of influenza A virus receiving multiple oral doses of JNJ-63623872 (up to 1,200 mg loading dose on the first day followed by 600 mg once daily for an additional 4 days) JNJ-63623872 was generally safe and well tolerated. Adverse events occurred in 63 of 72 (87.5%) subjects who received JNJ-63623872, and 28 of 32 (87.5%) subjects who received placebo. There were no SAEs or AEs leading to discontinuation of study drug:

- Influenza-like illness was the most frequent AE (pooled placebo, 37.5%; pooled JNJ-63623872, 47.2%), as expected due to viral inoculation. Adverse events that occurred in ≥10% of subjects and with ≥10% difference in the pooled JNJ-63623872 group than in the pooled placebo group were decreased blood phosphorus level (18.1% JNJ-63623872, 0% placebo), rhinorrhea (4.2% JNJ-63623872, 18.8% placebo), and nasal congestion (1.4% JNJ-63623872, 15.6% placebo).

- The majority of AEs that occurred in subjects treated with JNJ-63623872 were mild or moderate in severity. Some of the AEs were severe; 8 severe AEs occurred in 5 subjects treated with JNJ-63623872: decreased blood phosphorus (n=4); increased blood creatine phosphokinase (CPK) (n=1); increased blood myoglobin (n=1); and severe headache (n=2). The most frequent AEs considered possibly related to study drug in the pooled JNJ-63623872 group were increased alanine aminotransferase (ALT, 12.5%), decreased blood phosphorus (12.5%), and increased aspartate aminotransferase (AST, 5.6%). Both ALT elevation and serum phosphorus decrease have been previously described in influenza and other upper respiratory tract infections.

1.2. Oseltamivir

Oseltamivir (Tamiflu)

Oseltamivir is an influenza neuraminidase inhibitor indicated for the treatment of acute, uncomplicated influenza infection in patients 2 weeks of age and older who have been symptomatic for no more than 2 days and for prophylaxis of influenza in patients 1 year and older.

Clinical studies have shown that treatment with oseltamivir has clinical and virological benefit in patients with uncomplicated influenza when administered within 48 hours of onset of symptoms. Randomized studies in patients with severe influenza are lacking, but observational studies in patients admitted to hospital suggest that oseltamivir treatment, especially if it is given early, is associated with reduced mortality and shorter length of stay.[3]

Higher oseltamivir doses were tested in patients with uncomplicated influenza, but clinical or virological outcomes were found not significantly different compared to the standard dose. Despite a lack of evidence, several health authorities, including the United States Centers of Disease Control and Prevention (CDC) are recommending the use of double dose oseltamivir for severely ill or immunocompromised with influenza.[13]

There have been no studies specifically designed to evaluate the effectiveness of extending the duration of oseltamivir treatment beyond 5 days, however, it is reported in literature that over 32% of hospitalized patients carry replicating virus beyond 7 days of illness onset.[7] Using mathematical simulations to model an early or extended-duration oseltamivir therapy beyond 5 days has shown an increased virological and symptom efficacy and a potential for reduced emergence of resistance. The available data from uncomplicated influenza studies are inconclusive whether reducing viral shedding leads to faster clinical improvement, but there are data supporting that lower viral load results in faster symptom resolution.[7] Thus, there may be a possible benefit in using oseltamivir beyond 5 days in patients hospitalized with influenza.

For treatment of uncomplicated influenza in adults, oseltamivir is administered as 75 mg bid for 5 days without respect to food.[14,15] The dose is reduced in the presence of significant renal insufficiency. The most common AEs associated with oseltamivir (>1% and more common than with placebo) are nausea, vomiting, diarrhea, and abdominal pain. These events were generally mild to moderate and usually occurred on the first 2 days of administration. Subjects with influenza, including those receiving oseltamivir, may experience confusion and abnormal

behavior early in the course of illness. Serious skin/hypersensitivity reactions may occur with oseltamivir. Less than 1% of subjects discontinued prematurely from clinical studies due to nausea and vomiting.

Oseltamivir should not be administered until 2 weeks after intranasal live influenza immunization. Live influenza virus immunization should be delayed until 2 days after discontinuation of oseltamivir.

Oseltamivir is metabolized to oseltamivir carboxylate, which is pharmacologically active and entirely eliminated in the urine. Clinically significant drug interactions are unlikely. Plasma concentrations of the active metabolite are proportional to oseltamivir dose and display a small degree of inter-individual variability. Steady-state plasma concentrations were achieved within 3 days of administration of multiple doses. On the basis of AUC, there is less than 2-fold accumulation of the active metabolite during twice daily administration. Pharmacokinetic parameters after 1 week of administration of multiple doses provided no indication of a temporal change in the disposition of the active metabolite over time.

Following doses of 600 mg of JNJ-63623872 bid for 10 days, mean C_{max} and AUC_{12h} of JNJ-63623872 were, respectively, 1.2-fold and 1.8-fold higher on Day 10 compared with Day 1.[6]

JNJ-63623872 600 mg bid administered alone or in combination with oseltamivir 75 mg bid for 5 days resulted in generally comparable values for JNJ-63623872 predose plasma concentration (C_{0h}) on Days 3, 4, and 5, indicating that near steady-state conditions had been achieved prior to Day 3. For JNJ-63623872 administered alone versus in combination with oseltamivir, C_{min} and AUC_{12h} of JNJ-63623872 were comparable, while JNJ-63623872 C_{max} was 1.3-fold higher when administered in combination with oseltamivir, compared with administration of JNJ-63623872 alone. The median time to reach C_{max} (t_{max}) of JNJ-63623872 was 3.0 hours when JNJ-63623872 was administered alone and 1.5 hours when administered in combination with oseltamivir. For oseltamivir administered alone versus in combination with JNJ-63623872, oseltamivir AUC_{12h} and oseltamivir carboxylate C_{min}, C_{max}, and AUC_{12h} were comparable. Oseltamivir C_{min} was 1.1-fold higher and C_{max} was 5% decreased when administered in combination with JNJ-63623872, compared with oseltamivir administered alone.[6]

For further information regarding oseltamivir refer to the manufacturer's prescribing information.[14,15]

1.3. Overall Rationale for the Study

Although generally a self-limited disease, infection with influenza A can cause significant morbidity and mortality, especially in certain patient populations such as those at the extremes of age, and may result in hospitalization. Currently available antiviral therapies (oseltamivir [oral], zanamivir [inhaled] and peramivir [IV]) are not indicated for influenza in hospitalized patients; however, they are used as de-facto standard of care as recommended by the CDC and the World Health Organization (WHO) for this patient population. Another class of influenza antiviral drugs, the adamantanes, is also available but is associated with high levels of antiviral resistance among circulating influenza viruses.

The objective of antiviral therapy is to suppress viral replication rapidly and effectively, and thus provide a clinical benefit. Patients hospitalized with influenza are more severely ill and are reported to shed virus longer compared to patients with uncomplicated disease who are ambulatory. JNJ-63623872 has been demonstrated to neutralize a broad array of influenza A viruses both in in vitro and in vivo nonclinical models and has shown to reduce peak viral loads, AUC of viral shedding, and influenza-related clinical symptoms in an experimental human challenge model. A Phase 2b dose-ranging study evaluating JNJ-63623872 in adult subjects with uncomplicated seasonal influenza A infection is ongoing (VX14-787-103; 63623872FLZ2001).

The purpose of the current study is to evaluate the pharmacokinetics (PK), safety, and antiviral effect of JNJ-63623872 in elderly hospitalized subjects (aged 65 to ≤85 years) as compared to adult (aged 18 to ≤64 years) hospitalized subjects with influenza A following a 600 mg bid 7-day therapy.

In a mouse model of influenza infection, a concentration of 30 ng/mL was associated with effects on lung viral titers which were superior to those seen with oseltamivir, and 100 ng/mL was associated with even greater reductions in lung viral titers. Study 63623872FLZ1001 (VX787FLZ1001), a healthy adult volunteer drug-drug interaction and PK study, showed, in-line with previous PK modeling data, that JNJ-63623872 at a dose level of 600 mg bid resulted in a median C_{12h} of 161 ng/mL following the first dose and 310 ng/mL at steady-state. In this exploratory study, the dose regimen of 600 mg bid is expected to result in antiviral activity and a good safety profile.

1.4. Benefits and Risks Management

Please see Section 1.2 and the manufacturer's prescribing information[14,15] for the benefits and risks of oseltamivir.

1.4.1. Known Benefits of JNJ-63623872

The clinical benefit of JNJ-63623872 remains to be established.

1.4.2. Potential Benefits of JNJ-63623872

Results from JNJ-63623872 clinical studies may be useful in developing a new therapy for influenza A infection.

The dose regimen of 600 mg bid is expected to result in antiviral activity and subjects may benefit from participating in this study.

1.4.3. Known Risks of JNJ-63623872

Every medication can have undesirable effects.

Adverse events in healthy subjects: Based on the data available, only headache and diarrhea were seen consistently in healthy subjects and were considered by the investigator to be possibly related to JNJ-63623872 treatment. These events were generally mild to moderate. The occurrences of headache were equally distributed among JNJ-63623872 and placebo, while

diarrhea occurred more often after treatment with JNJ-63623872 compared to placebo. In subjects inoculated with influenza A virus in a challenge model of influenza A, transient elevations of liver transaminases, predominantly ALT, and decreased blood phosphorus were observed following JNJ-63623872 exposure.

1.4.4. Potential Risks of JNJ-63623872

Reproductive Risk and Pregnancy

Based on preclinical studies, no reproductive (embryo-fetal, fertility and early embryonic development) liabilities have been identified for JNJ-63623872.

In the current study, subjects who are heterosexually active must follow the contraception requirements detailed in Section 4.3. Subjects who are pregnant, or breastfeeding, or planning to become pregnant during this study or within 90 days after receiving the last dose of study drug, or are unwilling to use an acceptable method of contraception are not allowed to enter this study (see Section 4.2). Subjects' study treatment will be discontinued if they become pregnant (see Section 12.3.3).

Potential Toxicity

No genotoxicity (mutagenicity, in vitro chromosomal aberration, or mammalian erythrocyte), phototoxicity (in vitro), or safety pharmacology (battery of in vitro studies designed to evaluate effects of JNJ-63623872 against multiple cellular targets and a battery of in vivo cardiovascular, central nervous system, and respiratory systems) liabilities have been identified for JNJ-63623872. There were no toxicological effects in acute studies in mice and rats at doses up to 1,000 mg/kg. In studies where rats and monkeys were administered JNJ-63623872 at very high doses for 14 days, specific organ toxicity (liver, kidney, bone marrow, spleen, lymph nodes) and other toxicological findings were noted at doses of 250 mg/kg/day and above. The NOAEL in 14-day, repeat-dose toxicology studies was 100 mg/kg/day in rats and 150 mg/kg/day in monkeys. These doses correspond to animal to human exposure multiples ($AUC_{0\text{-}h}$ basis) of 40-fold and 24-fold in male and female rats, respectively, and 2-fold and 4-fold in male and female monkeys, respectively, based on a clinical dose of 600 mg bid for 5 days.

Based on human experience to date at high doses (up to 1,600 mg) no toxicology findings were observed, however this study will include study withdrawal criteria for individual subjects as a precaution (see Section 10.2, Discontinuation of Study Treatment).

1.4.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this study is acceptable for the following reasons:

- JNJ-63623872 has been studied in healthy subjects receiving single oral doses of JNJ-63623872 up to 1,600 mg (studies VX11-787-001 and VX12-787-002), multiple oral doses of JNJ-63623872 up to 800 mg once daily for 10 days (study VX11-787-001), multiple oral doses of JNJ-63623872 of 600 mg bid up to 10 days (study VX-787FLZ1001), and single IV doses of 100 mg JNJ-63623872 (study VX12-787-002), and in healthy subjects infected with a challenge dose of influenza A receiving multiple oral doses of JNJ-63623872 (up to 1,200 mg loading dose on the first day followed by 600 mg once daily for an additional 4 days) (study VX11-787-101). JNJ-63623872 was generally safe and well tolerated.
- Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
- Safety will be closely monitored by the investigator throughout the study. Safety and tolerability assessments (including vital signs, electrocardiogram [ECG], physical examination, clinical laboratory tests, and assessment of AEs or SAEs) will be performed at scheduled visits throughout the study.
- Several safety measures have been proposed to minimize potential risks to subjects, including:
  - A safety management plan is in place for subjects experiencing specific toxicities such as allergic reactions, clinical hepatitis, renal complications, nausea, and diarrhea.
  - The safety margins for the projected exposures calculated from non-clinical toxicology studies in monkeys warrant close laboratory monitoring during the study, thus samples for clinical laboratory tests will be collected throughout the study. Elevations of liver enzymes (eg, AST, ALT, bilirubin, gamma-glutamyltransferase [GGT], alkaline phosphatase [ALP]), hematological changes, serum creatinine elevations, and presence of proteinuria/albuminuria will be closely monitored.
  - Utilization of withdrawal criteria (see Section 10.2).
  - Pregnancy and breastfeeding are exclusion criteria for all clinical studies conducted to date. All subjects are required to use contraceptive methods as detailed in the protocol.
  - An independent data monitoring committee (IDMC) will be established to monitor safety and efficacy data on a regular basis.
- Oseltamivir is a widely used medication for the treatment of influenza A infection in patients 2 weeks of age and older. Please see Section 1.2 and the manufacturer's prescribing information[14,15] for the benefits and risks of oseltamivir.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to evaluate the PK parameters of JNJ-63623872 in combination with oseltamivir in elderly subjects (aged 65 to ≤85 years) compared to adults (aged 18 to ≤64 years) with influenza A infection.

Secondary Objectives

Secondary objectives include the assessment of the following parameters in the JNJ-63623872 treatment arm compared to the control arm:

1. Safety and tolerability.
2. The time to influenza viral negativity based on qRT-PCR and/or viral culture from nasal mid-turbinate (MT) swabs and, if applicable, based on PCR-based rapid molecular testing from nasal MT swabs.
3. Viral load over time and rate of decline in viral load during treatment as measured by qRT-PCR and/or viral culture.
4. AUC of viral load as measured by qRT-PCR and/or viral culture.
5. Disease status and incidence of complications associated with influenza after the start of study treatment, and disease progression:
   - bacterial pneumonia (culture confirmed where possible),
   - other bacterial superinfections,
   - respiratory failure,
   - pulmonary disease (eg, asthma, chronic obstructive pulmonary disease [COPD]),
   - cardiovascular and cerebrovascular disease (eg, myocardial infarction, congestive heart failure [CHF], arrhythmia, stroke).
6. Change in duration and severity of clinical symptoms as measured by the Flu-PRO.
7. Time to improvement of vital signs.
8. Time to improvement of respiratory status.
9. Improvement on the ordinal scale.
10. Emergence of drug resistance as detected by genotype or phenotype.
11. Time to return to premorbid functional status.
12. Time to hospital discharge.

Exploratory Objectives

Exploratory objectives include the assessment of the following parameters in the JNJ-63623872 treatment arm compared to the control arm:

1. Use of antibiotics and/or corticosteroids during hospitalization.
2. Number of subjects admitted to the Intensive Care Unit (ICU).
3. Length of ICU stay for subjects transferred to the ICU after baseline.
4. Correlation between the decline in viral load (measured by qRT-PCR and/or viral culture) and changes in clinical symptoms.
5. PK/PD relationship (efficacy and safety).

2.2. Hypothesis

No formal hypothesis will be tested.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the effect of JNJ-63623872 600 mg bid versus (vs.) placebo, both in combination with oseltamivir 75 mg bid in adult and elderly hospitalized subjects with influenza A infection. Up to 90 subjects in total will be enrolled in this study. An effort will be made to enroll a minimum of approximately 24 subjects per age cohort (adults aged 18 to ≤64 years and elderly people aged 65 to ≤85 years).

Subjects who meet all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- JNJ-63623872 600 mg bid + oseltamivir 75 mg bid; OR
- JNJ-63623872 placebo bid + oseltamivir 75 mg bid

Oseltamivir dose should be reduced to 30 mg bid for subjects with an estimated glomerular filtration rate (eGFR) >30 and ≤60 mL/min/1.73 m² according to the Modification of Diet in Renal Disease (MDRD) equation. Dose can be adjusted from 30 mg to 75 mg and vice versa during the course of treatment based on the eGFR value.

All study drugs will be taken orally.

The study will consist of a screening/baseline visit, a double-blind treatment period of 7 days, and a follow-up period of 21 days.

The entire study duration for each subject will be 28 days with study assessments daily during the treatment period, and on Days 10, 14, and 28 of the follow-up period. The study is considered complete with the completion of the last study assessment for the last subject participating in the study.

Full plasma concentration-time profiles of JNJ-63623872 will be determined over 12 hours after the morning dose of study drug on Day 3. For subjects who are discharged before Day 3, no intensive blood sampling will be performed. Sparse plasma samples for the measurement of

plasma concentrations of JNJ-63623872 will be taken on Days 1, 2, 4 through 7 during hospitalization, and on Days 5 and 8 after discharge (see Section 9.2, Pharmacokinetics). Measurement of plasma concentrations of oseltamivir and oseltamivir carboxylate may be done at the sponsor's discretion.

Safety and tolerability will be assessed throughout the study from signing of the Informed Consent Form (ICF) until the subject's last study-related activity. Safety evaluations will include the monitoring of AEs (including complications of influenza), clinical laboratory tests, 12-lead ECGs, vital sign measurements, (symptom-directed) physical examinations, pregnancy testing, and specific toxicities (see Section 9.3, Safety Evaluations).

Influenza symptom score, impact of influenza, and functional status will be assessed, and samples for viral titers and viral sequencing will be collected (see Section 9.4.1, Evaluations).

Blood samples will be collected to allow for the exploration of blood biomarkers (see Section 9.5). Where local regulations permit, an optional biomarker sample may be collected at baseline for host deoxyribonucleic acid (DNA) genotyping (see Section 9.7, Sample Collection and Handling).

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Refer to Section 11.8, Data Monitoring Committee, for details.

3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Arms

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Dose Selection

To date, three Phase 1 and one Phase 2 clinical studies have been completed. In the Phase 1 studies, a total of 128 healthy subjects were exposed to JNJ-63623872, receiving:

- a single oral dose of JNJ-63623872 ranging from 50 to 1,600 mg (studies VX11-787-001 and VX11-787-002, N=42),
- four single doses of 100 mg JNJ-63623872 (study VX11-787-001, N=16),
- 10-day multiple oral doses of JNJ-63623872 once daily ranging from 100 to 800 mg (study VX11-787-001, N=18),
- three single doses of 600 mg JNJ-63623872 (study VX12-787-002, N=18),

- single IV doses of 100 mg JNJ-63623872 (study VX12-787-002, N=8 previously exposed to single doses of 600 mg),
- 5-day multiple oral doses of JNJ-63623872 600 mg bid, alone or in combination with oseltamivir 75 mg (study 63623872FLZ1001, N=18; 4 additional subjects received up to 4 doses of 300 mg JNJ-63623872 twice daily),
- 10-day multiple oral doses of JNJ-63623872 600 mg bid (study 63623872FLZ1001, N=12).

In the Phase 2 study, 72 healthy subjects challenged with influenza A received multiple oral doses of JNJ-63623872, with a loading dose up to 1,200 mg on the first day followed by up to 600 mg once daily for an additional 4 days (study VX11-787-101). JNJ-63623872 was generally safe and well tolerated in these studies and no SAEs or AEs leading to discontinuation were observed. In addition, there were no clinically significant changes in standard 12-lead ECGs, vital signs, and clinical laboratory tests.

In an ongoing Phase 2b study (VX14-787-103; 63623872FLZ2001), the selected doses of JNJ-63623872 are 300 and 600 mg bid (without a loading dose). These doses were selected based on modeling and simulation.[9] Target concentrations of 30 and 100 ng/mL have previously been identified based on efficacy data in a mouse model of influenza infection, in which 30 ng/mL was associated with better efficacy compared to oseltamivir, and 100 ng/mL resulted in even greater reduction in viral load in the lungs. Simulations were performed to predict attainment of these target concentrations in patients. The probability of target attainment for simulated doses was compared to that of the highest dose evaluated in study VX11-787-101 (1200/600 mg once daily), at which a statistically significant improvement in viral shedding and clinical symptom scores was observed compared to placebo. The median plasma concentration just prior to the beginning or at the end of a dosing interval (C_{trough}) in the 1200/600 mg once daily dose group was approximately 130 to 150 ng/mL across the 5-day dosing duration. Twice daily doses were simulated with the goal of maintaining a higher C_{trough} without increasing the overall exposure or AUC.

In the current proposed study, JNJ-63623872 600 mg bid will be administered for 7 days to subjects infected with influenza A.

Host DNA and Biomarker Collection

Blood samples will be collected to allow for the exploration of blood biomarkers (eg, proteins, host RNA) on the premise that these markers may play a role in the blood concentrations, efficacy or safety of JNJ-63623872 or oseltamivir, or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to treatment. The biomarker analyses may also help to evaluate the PD of JNJ-63623872 and oseltamivir, and aid in evaluating the drug clinical response relationship. Where local regulations permit, an optional blood sample for exploratory host DNA research may also be collected.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4. SUBJECT POPULATION

Signing of the ICF needs to be done before the first study-related activity.

Screening for eligible subjects will be performed on Day 1, before the randomization and the first administration of study drug. ***Note:*** Day 1 encompasses signing of the ICF approximately + 24 hours, and can be split over 2 calendar days if needed. Depending on the time of hospital admission and the timing of screening/baseline assessments, eligibility may only be established on the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, see Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject requires hospitalization to treat influenza infection and/or to treat complications of influenza infection.

2. Subject tested positive for influenza A infection within 1 day of signing of the ICF using a PCR-based rapid molecular diagnostic assay.

3. Subjects must be capable of swallowing study medication tablets and capsules.

4. Subject must be male or female 18 to 85 years of age, inclusive.

5. Each subject (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

6. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (see Section 4.3, Prohibitions and Restrictions).

7. Before randomization, a female subject must be either:

    a. Not of childbearing potential:

        i. postmenopausal (>45 years of age with amenorrhea for at least 12 months);

        ii. permanently sterilized (eg, bilateral tubal occlusion [which includes tubal

ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy);

iii. or otherwise incapable of pregnancy.

b. Of childbearing potential and

i. practicing effective methods of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies

ii. and agrees to continue using two methods of birth control throughout the study and for at least 90 days after receiving the last dose of study drug (see Section 4.3, Prohibitions and Restrictions)

8. A female subject of childbearing potential must have a negative urine pregnancy test at screening.

9. A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction throughout the study and for at least 90 days after receiving the last dose of study drug (see Section 4.3, Prohibitions and Restrictions).

10. A male subject who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use effective methods of birth control(see Section 4.3, Prohibitions and Restrictions), and all male subjects must also not donate sperm during the study and for 90 days after receiving the last dose of study drug.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Subject received more than 3 doses of the influenza antiviral medication oseltamivir, zanamivir, or peramivir since the start of the influenza symptoms, or ribavirin within 6 months prior to screening.

2. Subject is unwilling to undergo regular nasal MT swabs or has any physical abnormality which limits the ability to collect regular nasal specimens.

3. Subject is known (considering lab results of the past 6 months) to be severely immunocompromised as defined by a $CD4^+$ count <350 cells/mm^3 or an absolute neutrophil count <750/mm^3.

4. Subject is undergoing peritoneal dialysis, hemodialysis, or hemofiltration.

5. Subject has an eGFR ≤30 mL/min/1.73m² according to the MDRD equation, assessed at

screening or based on the most recent clinically relevant creatinine value if available.

6. Subject has known moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C).

7. Subject has presence of any pre-existing illness, clinically significant laboratory abnormalities, ECG findings, or physical examination findings that, in the opinion of the investigator, would place the subject at an unreasonably increased risk through participation in this study. The investigator should consider the laboratory parameter criteria for study drug discontinuation (see Section 9.3.6) when screening a subject for enrollment.

8. Subject with known acute hepatitis A, B, or, C virus infection at screening, or known chronic hepatitis C infection undergoing antiviral therapy.

9. Subject has known allergies, hypersensitivity, or intolerance to JNJ-63623872 or its excipients (refer to the Investigator's Brochure[6]).

10. Subject has contraindications to the use of oseltamivir per local prescribing information.[14,15]

11. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days, or has received an investigational biological product within 3 months or 5 half-lives (whichever is longer) before the planned first dose of study drug or is currently enrolled in an investigational study.

12. Subject has a history of clinically significant heart arrhythmias, eg, unstable angina or myocardial infarction; uncontrolled, unstable atrial arrhythmia, or sustained ventricular arrhythmia, or a history of risk factors for Torsade de Pointes syndrome.

13. Subject has taken any disallowed therapies as noted in Section 8, Pre-study and Concomitant Therapy before the planned first dose of study drug.

14. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or a family member of an employee or the investigator, or an employee of the sponsor.

15. Female subject who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study drug, or female subject of childbearing potential who is unwilling to use an acceptable method of contraception as outlined in Section 4.3, Prohibitions and Restrictions.

16. Male subject who plans to father a child while enrolled in this study or within 90 days after the last dose of study drug.

17. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Female subjects of childbearing potential who are heterosexually active must remain on effective methods of birth control throughout the study and for at least 90 days after the last dose of study drug, and all female subjects must also agree not to donate eggs (ova, oocytes) throughout the study and for 90 days after receiving the last dose of study drug. Effective methods of birth control include use of an intrauterine device or hormone-based contraception in combination with a barrier contraceptive (eg, male condom, diaphragm with spermicidal gel, cervical cap, or female condom), or practice heterosexual abstinence. Female subjects of childbearing potential having a vasectomized partner are required to use one barrier contraceptive method throughout the study and for at least 90 days after the last dose of study drug when heterosexually active.

   Note: A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.
   Note: If the childbearing potential changes after start of the study (eg, female subject who is not heterosexually active becomes active), the subject must use effective methods of birth control, as described above throughout the study and for 90 days after the last dose of study drug.
2. Male subjects who are sexually active with a woman of childbearing potential and have not had a vasectomy must use effective methods of birth control as described above, and all male subjects must also not donate sperm throughout the study and for 90 days after receiving the last dose of study drug.

   If the female sexual partner is postmenopausal for at least 2 years, is permanently sterilized (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or otherwise incapable of becoming pregnant, the birth control methods mentioned are not applicable. If the female sexual partner has had a tubal ligation, at least one contraceptive method should be used.

   Male subjects who had a vasectomy and have a female partner of childbearing potential must agree to use a male condom throughout the study and for 90 days after receiving

the last dose of study drugs.

Note: A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.

3. Subject should refrain from taking any disallowed therapies as noted in Section 8, Pre-study and Concomitant Therapy.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment arms in a 2:1 ratio (active vs. placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by age cohort. An interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source documents. The documentation received

from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

6. DOSAGE AND ADMINISTRATION

During the treatment period, all subjects will receive 1 of the following 2 dose regimens:

- JNJ-63623872 600 mg bid + oseltamivir 75 mg bid on Days 1 through 7; OR
- JNJ-63623872 placebo bid + oseltamivir 75 mg bid on Days 1 through 7.

Note: For subjects who receive only 1 dose on Day 1 (evening), dosing should continue until the morning of Day 8 so that all subjects receive 14 doses in total.

Oseltamivir dose should be reduced to 30 mg bid for subjects with an eGFR >30 and ≤60 mL/min/1.73 m² according to the MDRD equation. Dose can be adjusted from 30 mg to 75 mg and vice versa during the course of treatment based on the eGFR value.

Study drugs (JNJ-63623872 or placebo + oseltamivir) will be administered according to the following guidelines:

- All study drugs will be taken together orally. All subjects will take 2 tablets (JNJ-63623872 or placebo) and 1 capsule (oseltamivir) bid.
- The first dose of study drugs will be administered on Day 1 (ie, signing of the ICF approximately + 24 hours) at the study site after screening assessments and randomization have been performed. Depending on the time of randomization and the time of first study drug intake on Day 1, subjects may receive 1 or 2 doses of study drug on Day 1. Subjects may delay or bring forward administration of the second dose (by no more than 4 hours) only if the nominal timing for this second dose falls in the middle of the night.
- Subjects will swallow the study drug whole and will not chew the drug before swallowing. Opening capsules or crushing tablets in food or water is not permitted.
- Study drug will be administered as described in the TIME AND EVENTS SCHEDULE. All intakes of study drug will take place at the study site for as long as subjects are hospitalized. Study-site personnel will instruct subjects on how to store study drug for at-home use in case subjects are discharged from the hospital during the treatment period.

For subjects who are discharged before Day 3, no intensive PK sampling will be performed.

7. TREATMENT COMPLIANCE

Missed doses (including those lost resulting from vomiting) will be recorded in the source documents and the eCRF, and re-dosed if the missed dose is discovered <6 hours past the scheduled dosing time. If the missed dose is >6 hours past the scheduled dosing time, the missed dose should be skipped, and the next dose should be taken as scheduled.

Subjects who are discharged during the treatment period, will receive study medication for at-home use. Compliance will be assessed at each visit by counting study drug dispensed and study

drug returned. Discrepancies will be discussed with the subject and recorded in the source documents and the eCRF.

If a subject's study drug intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 7 days before the first dose of study drug must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with the first dose of study drug until the Final Study Visit/Safety Follow-up Visit. Concomitant therapies should also be recorded beyond the Final Study Visit/Safety Follow-up Visit only in conjunction with SAEs that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

The following pre-study and concomitant therapies are disallowed:

1. More than 3 doses of the influenza antiviral medication oseltamivir, zanamivir, or peramivir **since the start of the influenza symptoms**.
2. Ribavirin **within 6 months of screening until the end of the study**.
3. Substrates of OATP1B1 and/or OATP1B3, including atrasentan, bosentan, ezetimibe, glyburide, irinotecan, repaglinide, rifampin, telmisartan, valsartan, and olmesartan, **from Day 1 through the last dose of study drug**. Statins (ie, HMG CoA reductase inhibitors) may be continued, but subjects should be cautioned and observed for potential statin-related toxicity.
4. An investigational agent (small molecule) or investigational vaccine within 30 days, or an investigational biological product within 3 months or 5 half-lives (whichever is longer) **prior to the first dose of study drug until the end of the study**.

Before the start of the study, the acute (< 7 days) use of corticosteroids (inhaled or systemic) is permitted; chronic (≥14 days) use of corticosteroids is permitted for prednisone doses ≤15 mg (or equivalent).

All use of antipyretic and anti-inflammatory agents for the treatment of influenza symptoms will be recorded. Subjects should restrict their use of anti-pyretic/anti-inflammatory medications only to acetaminophen (paracetamol) during the conduct of the study, and only when necessary to control significant influenza symptoms. The dose is not recommended to exceed 500 mg 3 times a day, and should preferably be administered immediately after the assessment of influenza symptoms. The use of other medications for the relief of influenza symptoms is strongly

discouraged. If the subject has an allergy or intolerance to acetaminophen (paracetamol), the investigator should recommend ibuprofen (at the lowest effective dose, but no more than 400 mg 3 times a day) as a substitute medication for the relief of influenza symptoms. If ibuprofen cannot be used, the investigator may use his/her discretion in the choice of agent.

For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented in the Adverse Event Section of the eCRF.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of PK sampling, safety, efficacy, biomarker, and patient-reported outcome (PRO) measurements applicable to this study.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood sampling. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documents and eCRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume to be collected from each subject will be approximately 125 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

In order to start treatment as soon as possible after the start of the influenza infection, screening will occur on Day 1, before randomization and the first administration of study drug. ***Note:*** Day 1 encompasses signing of the ICF approximately + 24 hours, and can be split over 2 calendar days if needed. Depending on the time of hospital admission and the timing of screening/baseline assessments, eligibility may only be established on the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility.

At the screening visit, after signing of the ICF (see Section 16.2.3, Informed Consent for more details), the overall eligibility of the subject to participate in the study will be assessed and documented in the eCRF. Subjects who successfully meet all inclusion criteria and none of the exclusion criteria will be eligible for participation in the study.

The subject's characteristics, demographic data, medical and surgical history, and prestudy and concomitant medication will be recorded. A PCR-based rapid molecular diagnostic assay capable of distinguishing between influenza types A and B will be carried out as part of the screening procedures. Only those subjects testing positive for influenza A will be considered for enrollment. A physical examination (including height and body weight measurements if not already available and if practically feasible) will be conducted. A urine pregnancy test will be performed for all female subjects of childbearing potential.

Subjects will be requested to complete ePRO assessments (Flu-iiQ^{TM}, Flu-PRO and additional daily diary items) to assess influenza-related signs and symptoms and the impact of influenza on the conduct of daily activities (see Section 9.4.1 for more details).

Blood samples (for hematology, biochemistry, blood coagulation parameters, drug concentrations, and biomarker analysis) and a urine sample (for urinalysis) will be taken. Where local regulations permit, an optional blood sample may be collected at baseline for host DNA genotyping. Nasal MT swabs will be obtained. Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, body temperature, and level of consciousness) and blood oxygen saturation will be measured, and a 12-lead ECG will be performed. A historical ECG within 1 day before signing of the ICF can be used in lieu of the baseline ECG requirement.

9.1.3. Double-Blind Treatment Phase

Subjects who meet all eligibility criteria will be randomized in a 2:1 ratio to receive 1 of the following 2 treatments:

- JNJ-63623872 600 mg bid + oseltamivir 75 mg bid on Days 1 through 7; OR
- JNJ-63623872 placebo bid + oseltamivir 75 mg bid on Days 1 through 7.

Note: For subjects who receive only 1 dose on Day 1 (evening), dosing should continue until the morning of Day 8 so that all subjects receive 14 doses in total.

Oseltamivir dose should be reduced to 30 mg bid for subjects with an eGFR >30 and ≤60 mL/min/1.73 m² according to the MDRD equation. Dose can be adjusted from 30 mg to 75 mg and vice versa during the course of treatment based on the eGFR value.

Subjects will undergo intensive PK sampling and sparse PK sampling at the time points specified in the TIME AND EVENTS SCHEDULE.

Throughout the treatment period, ePRO assessments will be completed before any other assessments for a specific visit; a symptom-directed physical examination, blood sampling (for

hematology, biochemistry, blood coagulation parameters, drug concentrations, and biomarker analysis), urine sampling (for urinalysis), and a urine pregnancy test (for females of childbearing potential) will be performed; nasal MT swabs will be obtained; vital signs and blood oxygen saturation will be measured; and a 12-lead ECG will be performed at the time points specified in the TIME AND EVENTS SCHEDULE.

Subjects should be observed/interviewed for any AEs (including complications of influenza), concomitant medication will be reviewed, and AEs and concomitant medication will be recorded.

Subjects, who are discharged during the treatment phase, will receive study medication for at-home use. Local PCR-based rapid molecular diagnostic testing will be carried out on the day of discharge and, if possible, on the day before.

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a safety follow-up visit. Subjects who withdraw consent during the treatment phase will be offered an optional safety follow-up visit. If the subject discontinues treatment due to an AE or other medical reason, efforts will be made by the investigator to continue following up with the subject at regular intervals until the AE normalizes or returns to the subject's baseline condition. The sponsor and the investigator will agree on an acceptable individual follow-up schedule for these subjects. Under this protocol, there will be no option to extend study treatment for subjects who remain hospitalized and symptomatic at the end of the 7-day treatment period. A subject will be considered to have completed treatment after 7-day therapy. It is up to the investigator's discretion to administer standard of care to hospitalized patients who in their opinion need additional therapy, outside of this protocol.

9.1.4. Posttreatment Phase (Follow-Up)

Subjects who prematurely discontinue the study for any reason (including withdrawal of consent) will be offered an optional safety follow-up visit. In case of ongoing AEs, efforts will be made by the investigator to continue following up with the subject at regular intervals until the AE normalizes or returns to the subject's baseline condition.

The procedures to be completed during the follow-up phase are listed in the TIME AND EVENTS SCHEDULE.

9.1.5. After discharge from the hospital

In case subjects are discharged from the hospital during the study, the remainder of the study visits should be carried out as outpatient visits (preferably on-site or, if not feasible, at the subject's home) or by telephone follow-up as indicated in the TIME AND EVENTS SCHEDULE. Every effort should be made to perform all of the assessments as outlined in the TIME AND EVENTS SCHEDULE (either on-site or at the subject's home) if practically feasible. Telephone contact will be made on Days 2-4 and 6-7 to ensure compliance with study drug intake, remind subjects to complete the ePRO assessments (and to perform nasal self-

swabbing if applicable), and to inquire about possible AEs and concomitant medication use. If the information on AEs and concomitant medications is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

9.2. Pharmacokinetics

9.2.1. Evaluations

Venous blood samples of approximately 1-2 mL will be collected for measurement of plasma concentrations of JNJ-63623872 (and, at the sponsor's discretion, for oseltamivir and oseltamivir carboxylate concentrations) at the time points specified in the TIME AND EVENTS SCHEDULE, and processed, handled and identified according to the laboratory manual, which will be provided before the start of the study. The exact dates and times of blood sampling and study drug intake must be recorded in the eCRF and/or laboratory requisition form. Measurement of plasma concentrations of oseltamivir and oseltamivir carboxylate may be done at the sponsor's discretion.

All hospitalized subjects will undergo **intensive PK sampling** on Day 3, at 8 different time points within the dosing interval. The first sample should be collected before (preferably immediately prior to) study drug intake (≤1 hour prior to the morning dose). Samples 2 to 8 should be collected at 1, 2, 4, 6, 8, 10, and 12 hours after the morning dose (and prior to the evening dose). For subjects who are discharged before Day 3, no intensive PK sampling will be performed.

During hospitalization, **sparse PK sampling** will be performed as follows:

- On Day 1: predose (≤1 hour prior to study drug intake), between 1.5 and 6 hours, and 12 hours after that same study drug intake (and prior to the next study drug intake). For subjects who start dosing in the morning of Day 1, a trough sample will be taken predose on Day 2 (≤1 hour prior to the morning dose).
- On Day 2 and Days 4-7: predose (≤1 hour prior to dosing) and between 1.5 and 6 hours after the morning or evening dose (whichever is the most convenient).

After discharge, sparse PK sampling will be performed as follows (if practically feasible):

- On Day 5: at any time during the visit.
- On Day 8: at any time during the visit.

As long as subjects are hospitalized, the following times need to be recorded in the eCRF:

- Date and time of all study drug intakes,
- Date and time of PK sampling,
- Date and start and stop times of food intake for all study drug intakes (if applicable).

After discharge, the above-mentioned dates and times will only need to be recorded on days with PK sampling.

For details on study drug intake, see Section 6.

9.2.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of JNJ-63623872 using a validated, specific, and sensitive (LC-MS/MS) method by or under the supervision of the sponsor. Measurement of plasma concentrations of oseltamivir and oseltamivir carboxylate may be done at the sponsor's discretion.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of oseltamivir and oseltamivir carboxylate, protein binding, and metabolite profile.

9.2.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-63623872 will be derived using non-compartmental analysis.

For JNJ-63623872

On Day 3: C_{trough}, $C_{min,}$ C_{max}, t_{max}, and AUC_{12h}

Additional PK parameters may be included if deemed appropriate. Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time of >20.00% deviation from the scheduled time, this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

9.2.4. Pharmacokinetic Endpoints

The PK endpoint, being the primary endpoint of this study is listed in Section 11.3.

9.2.5. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Evaluations

A population PK and PK/PD analysis of plasma concentration-time data of JNJ-63623872 will be performed using the nonlinear mixed-effects modeling approach. A more detailed description of the methodology to be followed will be given in the clinical pharmacology analysis plan (CPAP). Listings of JNJ-63623872 plasma concentration data from this study will be reported in the bioanalytical report for this study. Results of the population PK/PD analysis will be reported in a stand-alone document.

9.3. Safety Evaluations

Details regarding the IDMC are provided in Section 11.8.

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity.

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE:

9.3.1. Adverse Events

Adverse events (including influenza complications) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Special attention will be paid to those subjects who discontinue the study for an AE, or who experience an AE of at least grade 3, or an SAE.

9.3.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents.

If feasible, safety blood samples will be collected after fasting for at least 10 hours.

In case a **grade 3** or **grade 4** laboratory abnormality occurs, a confirmatory test may be performed, preferably within 48 hours but no later than 72 hours after the results have become available.

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -RBC parameters
  *mean corpuscular hemoglobin (MCH)
  *MCH concentration
  *mean corpuscular volume
  -white blood cell (WBC) count
  -WBC differential
  *neutrophils
  *lymphocytes
  *monocytes
  *eosinophils
  *basophils
  -platelet count

A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. Any RBC evaluation may include abnormalities in the RBC count and/or RBC parameters and/or RBC morphology, which will then be reported by the laboratory.

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-AST
-ALT
-GGT
-total, direct, and indirect bilirubin
-ALP
-CPK
-lactic acid dehydrogenase (LDH)
-uric acid
-eGFR
-calcium
-calcium (corrected for albumin)
-phosphate
-serum albumin
-total protein
-total cholesterol
-high-density lipoprotein cholesterol
-low-density lipoprotein cholesterol
-triglycerides
-magnesium
-lipase
-pancreatic amylase
-α_1-acid glycoprotein

- Urinalysis

Dipstick	Sediment (if dipstick result is abnormal)
-specific gravity	-RBCs
-pH	-WBCs
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-bilirubin	
-urobilinogen	
-nitrite	
-leukocyte esterase	

In case the dipstick shows 4+ (or >1.0%) proteinuria, a confirmatory test must be performed preferably within 48 hours but no later than 72 hours after the results have become available. If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time.

- At screening, at Day 5, and at the Final Study Visit/Safety Follow-up Visit, a urine pregnancy test will be performed for female subjects of childbearing potential only.

- At screening, follicle-stimulating hormone (FSH) will be tested for female subjects who are amenorrheic for 12 months or less.
- At screening, hepatitis A, B, and C serologic testing will be performed.
- At screening and at the time points indicated in the TIME AND EVENTS SCHEDULE, determination of the following coagulation parameters will be performed: prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. International normalized ratio (INR) will be calculated.

9.3.3. Electrocardiogram

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw. A historical ECG within 1 day before signing of the ICF can be used in lieu of the baseline ECG requirement.

Twelve-lead ECGs will be recorded so that the different ECG intervals (PR, QRS, and QT) and heart rate will be measured. The QT intervals will be corrected for heart rate according to Bazett's (QTcB) and Fridericia's (QTcF) QT correction.[5, 10]

Clinically relevant abnormalities occurring during the study should be recorded in the Adverse Event Section of the eCRF.

9.3.4. Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure, blood oxygen saturation, level of consciousness)

Vital signs including temperature, pulse/heart rate, respiratory rate, blood pressure, peripheral arterial blood oxygenation, and level of consciousness will be assessed once daily at screening and at the Final Study Visit/Safety Follow-up Visit. Vital signs will be assessed at least 3 times daily until the subject is discharged from the hospital or until Day 14 (whichever comes first): in the morning (prior to study drug intake if applicable), approximately half-way in the middle of the day, and in the evening (prior to study drug intake if applicable). If the subject is discharged from the hospital, vital signs will be measured once daily on Day 5 and Day 10, if practically feasible. In case, per standard practice, vital signs are measured more frequently than required per protocol, these additional measurements will also be recorded in the eCRF.

Temperature will be measured orally.

Blood oxygen saturation will be measured using standard pulse oximeter. Subjects should have nail polish removed and should be encouraged to sit still during the measurements.

Blood pressure, pulse/heart rate, and respiratory rate measurements should be preceded by at least 5 minutes of rest in the supine position in a quiet setting without distractions (eg, television, cell phones).

Blood pressure, pulse/heart rate, respiratory rate, and temperature measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

The level of consciousness will be measured according to the AVPU scale (alert, voice, pain, unresponsive).[8] Alert: The patient is fully awake (although not necessarily oriented). This patient will have spontaneously open eyes, will respond to voice (although may be confused), and will have bodily motor function. Voice: The patient makes some kind of response when you talk to them, which could be in any of the 3 component measures of eyes, voice, or motor. The response could be as little as a grunt, moan, or slight move of a limb. Pain: The patient makes a response on any of the 3 component measures on the application of pain stimulus, such as a central pain stimulus (sternal rub) or a peripheral stimulus (squeezing the fingers). Unresponsive: Sometimes seen noted as 'Unconscious'; this outcome is recorded if the patient does not give any eye, voice or motor response to voice or pain. The National Early Warning Score (NEWS) will be derived based on vital signs and AVPU scale at baseline and during hospitalization.[12]

Clinically relevant abnormalities (as defined in Attachment 7) occurring during the study should be recorded in the Adverse Event Section of the eCRF.

9.3.5. Physical Examination

To evaluate the subject's eligibility, a physical examination (including height and body weight measurement if not already available and if practically feasible) will be performed at screening. In addition, a symptom-directed physical examination will be performed at the time points provided in the TIME AND EVENTS SCHEDULE.

A physical examination includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated.

To obtain the actual body weight, subjects must be weighed lightly clothed. The height should be measured barefoot.

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event Section of the eCRF.

9.3.6. Specific Toxicities

Subjects reporting allergic reactions, AST/ALT elevations, clinical hepatitis, renal complications, nausea, or diarrhea, and other laboratory parameter changes should be followed until resolution of the AE or toxicity and necessary standard management should be undertaken.

Refer to Section 10.2 for study drug discontinuation criteria.

Acute Systemic Allergic Reaction

Cetirizine, levocetirizine, topical corticosteroids or antipruritic agents may be prescribed.

Subjects should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction.

Subjects will be treated as clinically appropriate.

AST and ALT Elevation

Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation (to be agreed upon with the sponsor).

Clinical Hepatitis

Subjects taking the study drugs should be monitored for the development of signs and symptoms of hepatitis which include fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum transaminase levels.

Subjects with these signs and symptoms must seek medical attention immediately and have hepatic parameters assessed. Relevant markers of viral hepatitis should also be assessed.

Renal Complications

If renal complications develop, subjects should be closely monitored for disturbances in serum creatinine and for abnormalities in urine analysis (eg, proteinuria). Additional investigations can be performed at the investigator´s discretion. Subjects must be treated as clinically appropriate.

Nausea (with or without Vomiting)

Subjects may be treated as needed with antiemetics given orally or rectally. The date and time of this AE should be recorded.

Diarrhea

Loperamide can be administered.

Other Laboratory Parameter Changes

If one (or more) of the following changes occurs, the subject should discontinue study drug and should be followed until resolution (return to baseline) or stabilization of change (to be agreed upon with the sponsor). The sponsor should be informed even if the change occurs outside of the treatment period (but before the end of the study).

- Liver enzymes - *screening/baseline*
  - AST or ALT enzyme activity increases ≥5 x ULN
  - Direct bilirubin increases ≥2 x ULN
  - GGT and/or ALP enzyme activity increases ≥3 x ULN

- Liver enzymes - *during treatment*
  - AST or ALT enzyme activity increases ≥5 x ULN if the baseline value is normal
  - AST or ALT enzyme activity increases ≥5 x baseline if the baseline value is >ULN
  - ALT enzyme activity increases >15 x ULN
  - ALT enzyme activity increases >3 x ULN and total bilirubin increases >2 x ULN
- Confirmed absolute neutrophil count <500/mm^3
- Hemoglobin <9 g/dL (female), <10.5 g/L (male)

9.4. Efficacy

9.4.1. Evaluations

9.4.1.1. Patient-reported Outcomes

Subjects should complete the PRO assessments (Flu-iiQ™, Flu-PRO and additional daily diary items) in their native language or if there is no version available in their native language, a version in a language in which the subject is fluent and literate. It is preferable that subjects are able to read and write to complete the assessments by themselves. If a subject is unable to read or has visual or other physical limitations that make it difficult to read or complete the assessments, trained study personnel may read the questions and responses aloud exactly as they appear on the assessment and record the subject's responses during the hospitalization phase. Once the subject is discharged from the hospital, if the subject is unable to complete the PRO assessment unaided, a caregiver can read the questions and responses verbatim and record the subject's responses for the subject.

Study personnel will instruct subjects how to self-administer the PRO tool and will record in the eCRF whether the PRO assessments were performed during the study visit. If subjects will require assistance recording their responses post-hospital discharge, study personnel will instruct the caregiver how to administer the PRO assessments.

Subjects will complete the PRO assessments electronically on a touch screen computer (ePRO device) provided for this study. The subject should be provided a quiet place to complete the PRO assessments, and instructed how to complete the PRO assessment on the ePRO device. When deciding which answer to report, subjects should not receive any help from anyone accompanying them (such as family members and friends) or study personnel; the responses should reflect the subject's interpretation and response.

Subjects' responses to the PRO questionnaires will not be reported as AEs or SAEs.

Influenza Symptom Score (Flu-iiQ™ Module 1)

Subjects will be asked to assess influenza-related signs and symptoms and other patient-reported outcomes and associated severity twice daily (preferably in the morning and in the evening) from study entry (Baseline, Day 1) through Day 14, and once daily (preferably in the evening) from

Day 15 through the Final Study Visit/Safety Follow-up Visit, using the Flu-iiQ™ influenza intensity and impact questionnaire (see Attachment 3) on an ePRO device.

Assessment of influenza symptoms will be recorded by the subjects or the site staff/caregiver if the subject requires assistance on the ePRO device and analyzed as an efficacy measure of treatment. Resolution of influenza symptoms will be the time since the start of treatment of the first of 2 evaluations (over 24 hours) in which all symptom scores for each of the 2 assessments are none or mild for all 7 primary influenza symptoms (cough, sore throat, headache, nasal stuffiness, feverishness or chills, muscle or joint pain, and fatigue).

Impact of Influenza (Flu-iiQ™ Modules 2, 3, 4)

The impact of influenza on conduct of daily activities will be assessed in Module 2 of the Flu-iiQ™ (see Attachment 3), scored on a 4-point scale, as above, for each of 6 activities. Scores will be assessed twice daily, at the same times as when the symptom scale evaluation is performed, from study entry (Baseline, Day 1) through Day 14, and once daily from Day 15 through the Final Study Visit/Safety Follow-up Visit. Assessments along with the additional daily diary items (see Attachment 4) will be recorded on the ePRO device. Time to resumption of usual activities is the time at which all scores are reported as "no difficulty".

Flu-PRO

The incidence and severity of symptoms (individual and composite) will be evaluated using the Flu-PRO questionnaire (see Attachment 5). Subjects will be asked to complete this questionnaire and additional daily diary items (see Attachment 6) on an ePRO device once daily (preferably in the evening) from study entry (Baseline, Day 1) through the Final Study Visit/Safety Follow-up Visit.

9.4.1.2. Viral Kinetics (Nasal MT Swabs)

Influenza viral titer will be determined and quantified in nasal MT swab samples taken at scheduled times throughout the study as indicated in the TIME AND EVENTS SCHEDULE. Nasal MT swabs will be analyzed using qRT-PCR and/or viral culture, and PCR-based rapid molecular testing. Influenza A subtype will be determined from the baseline sample.

When subjects are discharged from the hospital and still positive for influenza A virus, they are encouraged to continue self-swabbing at home if practically feasible.

Details about the nasal MT (self-) swab sample collection, processing, and shipping will be provided in the laboratory manual or other instruction documents.

The nasal MT swabs for central testing should be obtained from the left and the right nostrils and pooled into the same collection tube. Nasal MT (self)swabs for local PCR-based rapid molecular testing should be obtained from the left and the right nostrils (from both nostrils if feasible, but from only one nostril otherwise) and pooled into the same collection tube. Sampling should be done at approximately the same time when required. The investigator should designate a limited

number of trained study site personnel to collect the nasal MT swabs for the sake of consistency, and to train subjects on how to collect self-swabs if applicable.

9.4.2. Efficacy Endpoints

The efficacy endpoints, being the secondary endpoints of this study are listed in Section 11.6.

9.5. Resistance Evaluations

9.5.1.1. Viral Sequencing

Samples collected as described in Section 9.4.1.2 will also be used for sequence analysis of the PB2 region of the influenza virus polymerase and the neuraminidase gene at the time points specified in the TIME AND EVENTS SCHEDULE. Exploratory sequencing of other regions of the influenza virus genome may also be performed.

9.5.1.2. Phenotyping

Nasal MT swabs will be used for the analysis of phenotypic resistance against JNJ-63623872 and other antivirals at the time points specified in the TIME AND EVENTS SCHEDULE.

Details about sample collection, processing, and shipping will be provided in the laboratory manual.

9.6. Biomarkers

Two blood samples will be collected at the time points specified in the TIME AND EVENTS SCHEDULE for the exploration of blood biomarkers (eg, host RNA, proteins including serum cytokines) on the premise that these markers may play a role in the blood concentrations, treatment response, or safety of JNJ-63623872 or oseltamivir, or the status and change of the influenza virus related disease. Where local regulations permit, an optional blood sample may be collected for host DNA genotyping.

In addition, nasal MT swabs collected for other testing may be used for biomarker analyses if available.

Analyses of biomarkers (including DNA) may be conducted at the sponsor's discretion and reported separately from this study.

Blood samples for pharmacogenomic evaluations will preferably be collected at the baseline visit. However, if necessary eg, in case of a technical failure, they may be collected at a later time point without constituting a protocol deviation.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood

sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed all assessments of the Final Study Visit.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject undergoes mechanical ventilation
- The subject requires peritoneal dialysis, hemodialysis, or hemofiltration
- The subject has an eGFR ≤30 mL/min/1.73 m² according to the MDRD equation
- The subject experiences any of the laboratory abnormalities as specified in Section 9.3.6, Specific Toxicities.

If a subject prematurely discontinues study treatment, follow-up assessments should be obtained and scheduled assessments should be continued. If a subject drops out due to withdrawal of consent, he or she will be offered an optional Safety Follow-up Visit.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the treatment or the follow-up phase, he or she will be offered an optional Safety Follow-up Visit.

A subject who withdraws from the study will have the following options regarding the optional research sample:

- The collected sample will be retained and used in accordance with the subject's original separate ICF for optional research samples.
- The subject may withdraw consent for optional research sample, in which case the sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (see Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided. All demographic characteristics (eg, age, race, height, body weight, body mass index [BMI]) and other initial subject characteristics (physical examination, medical and surgical history, concomitant diseases, etc.) will be tabulated and analyzed descriptively.

11.2. Sample Size Determination

Up to 90 subjects in total will be enrolled in this study. An effort will be made to include at least 24 subjects for each cohort, with the total of subjects allowed to be recruited across both cohorts.

It is anticipated that it is feasible to recruit at least 60 subjects, which would lead to an acceptable precision for the primary objective.

For the primary objective of evaluating the PK of JNJ-63623872 across age cohorts the PK parameters considered of major importance are C_{min}, C_{max}, and AUC_{12h}. As there are no data available where Day 3 has been part of extensive PK sampling on the 600 mg bid dose, the variability on days with available data are presented in Table 2. Based on those data a between-subjects CV of 60% was assumed as a reasonably conservative estimate for the current study.

Table 2: Variability for Key Pharmacokinetic Parameters for JNJ-63623872 600 mg bid (Between-subjects %CV)

Time point	N	C_{min}	C_{max}	AUC_{12h}
Day 1	12	NA	65	56
Day 5	18	77	57	61
Day 5*	18	48	57	46
Day 10	12	56	44	43

Note: Based on study 63623872FLZ1001.
*JNJ-63623872 600 mg bid + oseltamivir 75 mg bid.
NA: Not applicable.

For age cohorts it was assumed that the number of hospitalizations would be about equal for elderly and non-elderly adults. In case 60 subjects are enrolled, there are 40 subjects on active treatment and it is assumed that at least 16 subjects are on active treatment in each cohort). For the comparison of PK parameters of the cohort of elderly adults (test) vs. non-elderly adults (reference) with PK data in a 16 to 24 ratio and a between-subject coefficient of variation (CV) of 60%, the 90% confidence interval (CI) of the geometric mean ratio (GMR) for C_{min} would be predicted to have a half-width of 35%, indicating that we can be 90% confident that the true GMR is in the interval observed GMR/1.35 to 1.35*GMR. If 90 subjects were enrolled with 60 on active treatment in a 24 to 36 ratio, the predicted half-width would be 28%.

The precision was expressed as the half-width of the 90% confidence band around the predicted mean LOESS estimate (illustrated in a simulated situation presented in Figure 1, with circles as the individually simulated values for C_{min}, as a solid line the predicted values and the shaded area the 90% confidence band for the prediction). With the anticipated numbers of subjects, the average half-widths and the maximum half-width are presented in Table 3 as percentages. The average half-width is the relative distance between the prediction and the 90% confidence band around that mean, averaged across the observed data points. Based on 40 to 60 subjects exposed to JNJ-63623872, the 90% confidence band for the planned LOESS regression was considered sufficiently precise (with average half-widths less than 25%) in order to evaluate the relationship between age and the major PK parameters.

Figure 1: Example of LOESS Regression for a Simulated Data Set for C_{min} (N=50)

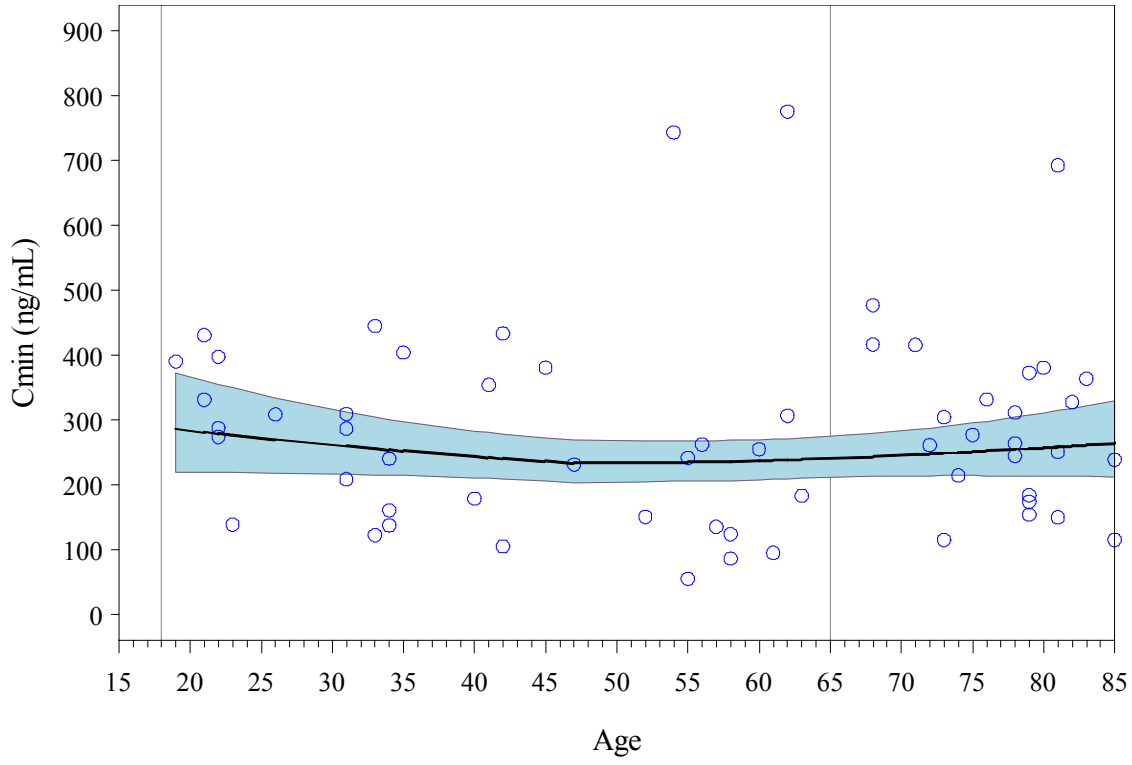

Table 3: Precision of the LOESS Confidence Band Around the Prediction

C_{min} (CV=60%)	Number of subjects treated with JNJ-63623872		
	N=40	N=50	N=60
Mean half-width*	25%	22%	20%
Maximum half-width*	46%	40%	36%

*Expressed as the ratio of the upper 90% confidence band divided by the prediction derived from the LOESS regression. Expressed as a percentage, based on 10.000 simulations.

For the safety objective of the study the sample size of 40 to 60 subjects treated with JNJ-63623872 can be characterized by assessing the precisions for (potentially) observed treatment-emergent AEs. For example, if no related treatment-emergent SAE is observed in a sample of 60 subjects exposed to JNJ-63623872, it can be concluded with 95% confidence that the true incidence of related treatment-emergent SAEs will be less than 5%. Table 4 presents the one-sided upper confidence limits for a range of numbers of treated subjects.

Table 4: Upper Confidence Limits for any Event with a Zero Incidence

	Number of subjects treated with JNJ-63623872		
	N=40	N=50	N=60
Upper confidence limit*	7.2%	5.8%	4.9%

*Upper 95% confidence limit (one-sided) using the Clopper-Pearson method

Besides characterizing the precision for excluding significant side-effects, the current study also allows to assess the incidence of treatment-emergent AEs on JNJ-63623872 vs. placebo treatment. Table 5 presents the 95% CIs for the risk difference that may potentially be observed.

For example, with 4 events (out of 60) vs. 1 event (out of 30) the risk difference (95% CI) would be 3.3% (-19%, 26%).

Table 5: Risk Differences and Associated 95% Confidence Intervals for Potential Treatment-emergent Adverse Event Incidences

Risk difference (95% CI) by sample size (active: placebo)		
40:20	50:25	60:30
0% (-28%, 28%)	0% (-25%, 25%)	0% (-22%, 22%)
2.5% (-25%, 30%)	2.0% (-23%, 27%)	1.7% (-21%, 24%)
5.0% (-23%, 32%)	4.0% (-21%, 28%)	3.3% (-19%, 26%)
7.5% (-20%, 35%)	6.0% (-19%, 30%)	5.0% (-18%, 27%)
10.0% (-18%, 37%)	8.0% (-17%, 32%)	6.7% (-16%, 29%)

Based on exact 95% confidence intervals. Interval width only depends on risk difference. For zero events in both groups the confidence interval for the risk difference is not defined.

11.3. Pharmacokinetic Analyses

Pharmacokinetic parameters will be used to assess the exposure of JNJ-63623872 on Day 3. Refer to Section 9.2 for more details.

Primary Endpoint

- PK parameters of JNJ-63623872 (ie, C_{min}, C_{max}, and AUC_{12h}) established on Day 3.

Intensive Pharmacokinetic Sampling (Day 3)

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be calculated for plasma concentrations of JNJ-63623872 at each sampling time point and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation (SD), %CV, geometric mean, median, minimum, and maximum.

For each subject treated with JNJ-63623872, JNJ-63623872 plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis in order to get a general overview.

Statistical analysis will be performed for the PK-evaluable population. Elderly adults (65 to ≤85 years) will be compared vs. non-elderly adults (reference) to investigate the relative effect of age. The primary PK parameters are C_{max}, C_{min}, and AUC_{12h}. AUC_{12h} will be rejected as primary parameter for an age cohort if more than half of the subjects of that age cohort do not have a reliable value. For the primary PK parameters, the GMR of test vs. reference will be calculated including the associated 90% CI.

For the assessment of an age effect, regression techniques will be employed to describe and predict the relation between age and primary PK parameters. As the relationship need not be linear across age, LOESS regression will be used that allows for a nonlinear model fit. The LOESS model uses smoothing based on goodness of fit criteria; recognizing that marked local changes are not biologically plausible, smoothing will be restricted. In case important predictive covariates are identified a generalized additive model will be used to model the relation between age and PK parameters adjusted for covariates, including LOESS regression for age. Regression will be performed on the logarithm of the PK parameter, with the results of the regression being retransformed to the original scale, including the 90% confidence band around the regression line. For an effect of body weight on primary PK parameters a similar approach will be used as an exploratory analysis.

Special attention will be paid to the plasma concentrations and PK parameters of those subjects who have discontinued the study for an AE, or who experienced an AE of at least grade 3, or an SAE.

Sparse Pharmacokinetic Sampling

Population PK analysis of plasma concentration-time data of JNJ-63623872 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, body weight, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-63623872 and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all subjects with available plasma concentrations per treatment arm. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment arm, descriptive statistics, including sample size (n), arithmetic mean, SD, %CV, geometric mean, median, minimum, and maximum will be calculated for all individually derived PK parameters including exposure information of JNJ-63623872.

11.4. Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of JNJ-63623872 exposure (AUC_{12h}, C_{max}, or C_{min}) with efficacy (ie, change in viral load from baseline and virologic response) and safety (including AEs and laboratory abnormalities) will be explored. Other exploratory analyses may be performed.

11.5. Safety Analyses

All safety endpoints will be evaluated on the Safety population, consisting of all subjects who received at least one dose of study drug and will be analyzed by drug received. Safety will be evaluated by means of AEs (including complications of influenza), clinical laboratory tests, ECGs, vital signs, NEWS, physical examinations, pregnancy testing, and specific toxicities. The safety analysis will be done for the Safety population and for each study phase separately (treatment, follow-up, and the combination of both).

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm. In addition, comparisons between treatment arms will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious AE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- vs. post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The laboratory abnormalities will be determined according to the criteria specified in the WHO grading table (see Attachment 1) and in accordance with the normal ranges of the clinical laboratory if no gradings are available. Laboratory abnormalities will be tabulated by scheduled time point.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline) to allow detection of clinically relevant changes in individuals.

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval using the following correction methods: QTcB, QTcF, and QT correction derived by linear regression (QTcL).[5,9]

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All important abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

The percentage of subjects with abnormalities will be tabulated by treatment arm.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, blood pressure (systolic and diastolic) (supine), arterial oxygen saturation values, level of consciousness, and changes from baseline will be summarized at each scheduled time point. For oxygen saturation an overview will be presented for the number of subjects that require supplemental oxygen. The percentage of subjects with values beyond clinically important limits will be summarized. For each subject, the NEWS will be derived based on the vital sign data. The average of the NEWS over time will be presented by treatment group.

Electrocardiogram data will be summarized by vital sign parameters (temperature, pulse/heart rate and blood pressure [systolic and diastolic]). Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

11.6. Efficacy Analyses

The efficacy endpoints will be analyzed on the Full Analysis Set, consisting of all subjects who were randomized, treated and had a confirmed influenza A infection, and will be analyzed by drug received.

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and by age cohort. No formal statistical hypothesis testing will be made.

Clinical outcomes

The incidence of influenza complications will be categorized in a hierarchical fashion. The overall category will consist of any complication, consisting of the following subcategories:

- bacterial pneumonia (culture confirmed where possible),
- other bacterial superinfections,
- respiratory failure,
- pulmonary disease: asthma, chronic obstructive pulmonary disease [COPD]),
- cardiovascular and cerebrovascular disease (eg, myocardial infarction, congestive heart failure [CHF], arrhythmia, stroke),
- post-baseline ICU admission,
- all-cause mortality

The incidences on Day 28 of each (sub) category will be analyzed using logistic regression; baseline characteristics that are predictive of the incidence of complications can be included based on goodness of fit criteria. Odds ratios and associated 95% CIs will be reported of active vs. control treatment.

The time to improvement of vital signs is defined as the time from first study treatment to when at least 4 of 5 symptoms (temperature, blood oxygen saturation, heart rate, SBP, respiration rate) are recovered, including normalization of temperature and blood oxygen saturation. Normalization is defined in Table 6. If subjects satisfy these criteria at entry they will be censored at that time (effectively they will be excluded from the analysis). The data will be presented using a Kaplan-Meier curve. The time to event data will be modeled using the accelerated failure time (if the data provide an acceptable model fit) or alternatively a Cox proportional hazards model (in case the hazards are proportional). Additionally, the time to event data will be analyzed using the Gehan-Wilcoxon method.

Table 6: Resolution Criteria for Vital Signs

Assessment	Resolution Criterion
Temperature	≤ 37.2 °C or ≤ 37.8 °C rectal or tympanic
Oxygen saturation	≥ 92% on room air without supplemental oxygen
Respiration rate	≤ 24/min
Heart rate	≤ 100/min
Systolic blood pressure	≥ 90 mmHg

Time to improvement of respiratory status is defined as normalization of blood oxygen saturation and respiration rate. Analysis performed will be analogous to the analysis for the time to improvement of vital signs.

The ordinal scale consists of 6 categories that are exhaustive, mutually exclusive, and ordered (Table 7). For all patients, the category at Day 8 will be established as the worst category on that day. For example, if someone is discharged on Day 8, the category will be non-ICU and no supplemental oxygen (if there was no supplemental oxygen given on that day). The analysis will be performed using a proportional odds model, modeling the common odds ratio of the improvement on the ordinal scale of active treatment versus control. Baseline covariates that are predictive of the ordinal scale may be added to the model to increase the model fit. In case of missing data (>10%), a multiple imputation method under the missing-at-random assumption will be employed. Details will be provided in the Statistical Analysis Plan.

Table 7: Ordinal Scale on Day 8

Outcome
Death
Admitted to ICU or mechanically ventilated/ECMO
Non-ICU + supplemental oxygen
Non-ICU + no supplemental oxygen
Not hospitalized, but unable to continue activity
Not hospitalized and continues activities

ECMO = extracorporeal membrane oxygenation; ICU = Intensive Care Unit

Viral kinetics

Measures of viral kinetics are performed for both qRT-PCR and viral culture of nasal MT swabs:

- Duration of viral shedding defined as time to influenza A viral negativity
- Viral AUC calculated from baseline to Day 14
- Rate of decline of viral load
- Incidence of influenza A viral negativity by assessment
- Peak viral shedding titer

The time to influenza A viral negativity will be determined based on nasal MT swabs: a subject will be considered influenza A viral negative at the time point that the first negative nasal MT swab was recorded (in days). A subject will be censored at the time of the last observed non-negative swab + 1 day. The time to influenza A viral negativity will be summarized using a Kaplan-Meier curve. The accelerated failure time model will be used to compare the time to recovery for JNJ-63623872 vs. control treatment; the accelerated failure time model will use a Weibull, log-logistic, lognormal or gamma distribution based on goodness of fit criteria. Additionally, the time to event data will be analyzed using the Gehan-Wilcoxon method. The AUC will be estimated for each treatment arm using a mixed model for repeated measurements, ie, the AUC will not be calculated for each subject and then analyzed, but the AUC will be calculated for each treatment arm using the viral data over time of each subject. This approach ensures an optimal approach towards missing data. The rate of decline in quantitative viral load

will be estimated through a pre-specified linear mixed model. The incidence of viral negativity will be analyzed using logistic regression. For the peak viral shedding titer a GMR will be derived using a general linear model. For each analysis the difference between the treatment arms will be presented including the associated 95% CI. Factors that are predictive of viral titers will be included as covariates.

Patient-reported Outcomes

The time to resolution of influenza symptoms will be the time of the first of 2 evaluations (over 24 hours) in which all symptom scores for each of the 2 assessments are none or mild for the 7 primary influenza symptoms as recorded in the Flu-iiQ™ (cough, sore throat, headache, nasal stuffiness, feverishness or chills, muscle or joint pain, and fatigue).

The FLU-PRO and Flu-iiQ™ domain scores will be presented descriptively over time using descriptive statistics. A linear mixed model will be used to analyze composite symptom scores over time, per domain. For the Flu-iiQ™ a daily score will be derived averaging observed scores before the analysis. Baseline subject characteristics will be included (in particular baseline score) in case these provide to be predictive of post-baseline scores. Mean differences between treatment arms will be derived from this model using appropriate contrasts and will be presented including the associated 95% CI. For both measures, an AUC of composite symptom scores over a 7- and 14-day period per domain will be calculated and compared using a mixed model for repeated measurements.

Other PRO endpoints that will be analyzed are:

1. Time to return to usual activity and usual health (Questions 5 and 9 of the additional items for the Flu-PRO).
2. Time to significant reduction in influenza symptom severity.
3. Proportion of patients with a significant reduction (to mild or none for all influenza symptoms) at each assessment.

Other Outcomes

The length of overall hospital stay will be calculated from the date of first study drug intake up to the date of discharge. Subjects still hospitalized at the end of the study will be censored at the last contact. Data will be presented using Kaplan-Meier curves. For a comparison between treatment arms, the time to hospital discharge in days will be analyzed using an accelerated failure time model (if the data provide an acceptable model fit) or alternatively a Cox proportional hazards model (in case the hazards are proportional). Additionally, the time to event data will be analyzed using the Gehan-Wilcoxon method. The time to resumption of normal daily activities will be analyzed in an analogous fashion.

Resistance Analyses

The results of viral sequencing and phenotyping will be evaluated by the sponsor virologist. Additional exploratory characterization of the viral genotype and phenotype may be performed and will be reported accordingly.

11.7. Biomarker Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between study subjects. Analyses may be conducted at the sponsor's discretion and reported separately from this study.

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (treatment response, side effects, metabolism) and possibly relevant genes at the time of analysis. Analyses may be conducted, if deemed valuable, at the sponsor's discretion and may be reported separately from this study.

11.8. Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

An interim analysis may be performed to support regulatory activities.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (see Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-63623872, since no adverse drug reactions are currently identified in the Investigator's Brochure, all related SAEs are considered unexpected for reporting purposes. For oseltamivir with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the manufacturer’s prescribing information.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale in Attachment 1.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug

- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported electronically via Electronic Data Capture (eDC) or via facsimile (fax) when applicable using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events, including influenza complications that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source documents and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source documents and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event page of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically via eDC or via fax when applicable.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). ***Note:*** Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (see Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate Pregnancy Notification Form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported electronically via eDC or via fax when applicable using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate Pregnancy Notification Form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (see Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The JNJ-63623872 supplied for this study is formulated as: 300-mg tablets for oral administration, containing JNJ-63623872, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K30, sodium stearyl fumarate, Opadry II, white.

A second formulation also containing the equivalent of 300 mg of JNJ-63623872 free base has been developed by the sponsor, which is also suitable for use in this study. The tablet contains hypromellose, polysorbate 20, crospovidone, silica colloidal anhydrous, silicified microcrystalline cellulose, microcrystalline cellulose, pregelatinized starch, sodium stearyl fumarate, Opadry II yellow.

JNJ-63623872 formulations are manufactured and provided under the responsibility of the sponsor. The JNJ-63623872 formulation to be used in each different country is determined by which one is approved by each respective health authority.

Matching JNJ-63623872 placebo tablets for each of the active formulations are available and will be provided for subjects randomized to the placebo group.

Commercially available supplies of oseltamivir will be used, formulated as: 75-mg capsules or 30-mg capsules for oral administration, containing oseltamivir phosphate, pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate.

14.2. Packaging

The study drug (JNJ-63623872 or matching placebo tablets and oseltamivir capsules) will be provided on a blister card for each subject.

No study drugs can be repacked without prior approval from the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

Commercial oseltamivir capsules will be labeled with a study-specific label under the responsibility of the sponsor.

No study drugs can be relabeled without prior approval of the sponsor.

14.4. Preparation, Handling, and Storage

All study drug must be stored as specified on the label.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. In case subjects are discharged from the hospital during the treatment period, the dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug (and study drug returned by the subject, where applicable) must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug (or used returned study drug for destruction) will be documented on the Drug Return Form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure of JNJ-63623872
- Prescribing information for oseltamivir
- Pharmacy manual/study site investigational product manual
- Laboratory manuals (including procedures for collection of nasal swabs)
- Contact information page(s)

- ePRO device and user manual
- IWRS Manual
- eDC Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and pharmacogenomic research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-63623872 and oseltamivir, to understand influenza A infection, to understand differential drug responders, and to develop tests/assays related to JNJ-63623872 and oseltamivir and influenza A infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (see Section 10.3, Withdrawal From the Study [Withdrawal From the Use of Samples in Future Research]).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page[s] provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be

obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits (including telephone follow-up calls, if applicable); results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The PRO assessments (Flu-iiQ^{TM}, Flu-PRO and additional daily diary items) will be completed by subjects on an ePRO device. The results will be recorded directly into the ePRO database and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents into the eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into CRFs in

English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory into the sponsor's database, and direct transmission of PRO data to the ePRO vendor database and then into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the hospital or clinic records (source documents) for completeness and accuracy, and perform source data verification to any source data captured on paper and entered in the system later. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-63623872 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated

as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-63623872, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study, laboratory data from the selected laboratory that were transmitted to the sponsor's database, and PRO data from the ePRO vendor database that were transmitted to the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant

contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (Feb 2003)

ABBREVIATIONS (used in the table):

ULN = Upper Limit of Normal

LLN = Lower Limit of Normal

R_x = Therapy

IV = Intravenous

FEV_1 = forced expiratory volume in 1 second

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (<48 hours); no medical intervention/therapy required.
GRADE 2	**Moderate**	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required.
GRADE 3	**Severe**	Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalizations possible.
GRADE 4	**Potentially life-threatening**[a]	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable.

[a] Revised by the sponsor

COMMENTS REGARDING THE USE OF THESE TABLES

- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system. Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin	9.5-10.5 gm/dL	8.0-9.4 gm/dL	6.5-7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000-1,500/mm³	750-999/mm³	500-749/mm³	<500/mm³
Platelets	75,000-99,000/mm³	50,000-74,999/mm³	20,000-49,999/mm³	<20,000/mm³
Prothrombin Time (PT)	≥1.01 to ≤1.25 x ULN	>1.25 to ≤1.50 x ULN	>1.50 to ≤3.00 x ULN	>3.00 x ULN
Activated Partial Thromboplastin Time (aPTT)	≥1.01 to ≤1.66 x ULN	>1.66 to ≤2.33 x ULN	>2.33 to ≤3.00 x ULN	>3.00 x ULN
Fibrinogen	≥0.75 to ≤0.99 x LLN	≥0.50 to <0.75 x LLN	≥0.25 to <0.50 x LLN	<0.25 x LLN
Fibrin Split Product	20-40 mcg/mL	41-50 mcg/mL	51-60 mcg/mL	>60 mcg/mL
Methemoglobin	5.0-9.9%	10.0-14.9%	15.0-19.9%	>20.0%
Liver Enzymes				
AST (SGOT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
ALT (SGPT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Gamma-glutamyltransferase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Alkaline Phosphatase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Amylase	≥1.1 to ≤1.5 x ULN	>1.5 to ≤2.0 x ULN	>2.0 to ≤5.0 x ULN	>5.0 x ULN
Chemistries				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement Rx required or hospitalization required	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (corrected for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL or life-threatening arrhythmia
Hypomagnesemia	1.4-1.2 mEq/L	1.1-0.9 mEq/L	0.8-0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL or replacement Rx required	1.0-1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	≥1.1 to ≤1.5 x ULN	>1.5 to ≤2.5 x ULN	>2.5 to ≤5.0 x ULN	>5.0 x ULN
BUN	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Creatinine	≥1.1 to ≤1.5 x ULN	>1.5 to ≤3.0 x ULN	>3.0 to ≤6.0 x ULN	>6.0 x ULN or required dialysis
Urinalysis				
Proteinuria	1+ or <0.3% or <3g/L or 200 mg – 1 gm loss/day	2-3+ or 0.3-1.0% or 3-10 g/L or 1-2 gm loss/day	4+ or >1.0% or >10 g/L or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
Cardiac Dysfunction				
Cardiac Rhythm	-	asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires Rx
Hypertension	transient inc. >20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

Item	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory				
Cough	transient; no Rx	treatment associated cough; local Rx	uncontrolled	-
Bronchospasm, Acute	transient; no Rx <80-70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50-70% (or peak flow)	no normalization with bronchodilator; FEV_1 25-50% (or peak flow retractions)	cyanosis: FEV_1 <25% (or peak flow) or intubated
Gastrointestinal				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
Neuro & Neuromuscular				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and Rx required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; Rx required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

Item	Grade 1	Grade 2	Grade 3	Grade 4
Other Parameters				
Fever: oral, >12 hours	37.7-38.5 °C or 100.0-101.5 °F	38.6-39.5 °C or 101.6-102.9 °F	39.6-40.5 °C or 103-105 °F	>40 °C or >105 °F
Headache	mild, no Rx	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25-50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration <10 cm or phlebitis or inflammation	induration >10 cm or ulceration	necrosis
Mucocutaneous	Erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement, or erythema multiforme or suspected Stevens-Johnson or necrosis requiring surgery

Attachment 2: Anticipated Events

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Bacterial pneumonia
- Bronchitis
- Sinus infections
- Ear infections
- Worsening of asthma, asthma attack
- COPD exacerbation
- Complications of sickle cell disease, sickle cell crisis
- Complications of diabetes mellitus, diabetic ketoacidosis
- Acute respiratory distress syndrome (ARDS)

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets SAE criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

In this study, the IDMC will perform the role of an Anticipated Event Review Committee (ARC) and will conduct reviews of pre-specified anticipated events at an aggregate level. The IDMC will provide the recommendation to the Sponsor Committee as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 3: Influenza Intensity and Impact Questionnaire (Flu-iiQ™)

This attachment provides a representative example of the Flu-iiQ™ questionnaire that will be used in this study.

Measured Solutions for Health P/L (MESH)
PO Box 5127 Alphington 3078
Victoria Australia
Telephone +61 (0)4000 355 29
measuredsolutions@bigpond.com
ABN 16 105 383 640

Influenza intensity and impact questionnaire (Flu-iiQ™)

Please read each question below and check one box that best describes your symptoms.

Complete the questionnaire when you rise from bed in the morning and right before you go to bed at night.

1. Because of influenza do you have any of the following symptoms now?

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Loss of appetite	☐	☐	☐	☐

Influenza intensity and impact questionnaire (Flu-iiQ™) ©RH Osborne (2006). No part of the Flu-iiQ™ may be copied or reproduced in any form without written permission from the author: measuredsolutions@bigpond.com

IMPACT OF INFLUENZA

2. Does influenza affect your ability to do any of the following activities now?

	No Difficulty	Some Difficulty	Moderate Difficulty	Great Difficulty
a. Get out of bed	☐	☐	☐	☐
b. Prepare meals / get your own food	☐	☐	☐	☐
c. Perform usual activities	☐	☐	☐	☐
d. Leave the home	☐	☐	☐	☐
e. Concentrate on tasks	☐	☐	☐	☐
f. Take care of yourself	☐	☐	☐	☐

3. Does influenza currently make you:

	Not at all	Somewhat	Moderately	Extremely
a. Irritable	☐	☐	☐	☐
b. Feel helpless	☐	☐	☐	☐
c. Worried	☐	☐	☐	☐
d. Frustrated	☐	☐	☐	☐

4. Because of influenza are you currently concerned about:

	Not at all concerned	Somewhat concerned	Moderately concerned	Extremely concerned
a. People worrying about you	☐	☐	☐	☐
b. Being a burden	☐	☐	☐	☐
c. People being annoyed with you	☐	☐	☐	☐
d. Needing to depend on people	☐	☐	☐	☐
e. People having to do extra things for you	☐	☐	☐	☐

Influenza intensity and impact questionnaire (Flu-iiQ™) ©RH Osborne (2006). No part of the Flu-iiQ™ may be copied or reproduced in any form without written permission from the author: measuredsolutions@bigpond.com

Attachment 4: Additional Daily Diary Items to Flu-iiQ™

This attachment provides a representative example of the additional daily diary items to Flu-iiQ™ that will be used in this study.

63623872FLZ2002 Additional daily diary items to Flu-iiQ™ Version 1.0 dd 31JUL2015

Items to be asked in addition to the Flu-iiQ™.

1. Does influenza affect your ability to perform any of the activities now?

a) Eat meals

☐4 No Difficulty
☐3 Some Difficulty
☐2 Moderate Difficulty
☐1 Great Difficulty

b) Go outside by yourself

☐4 No Difficulty
☐3 Some Difficulty
☐2 Moderate Difficulty
☐1 Great Difficulty

c) Take a shower

☐4 No Difficulty
☐3 Some Difficulty
☐2 Moderate Difficulty
☐1 Great Difficulty

d) Climb a flight of stairs

☐4 No Difficulty
☐3 Some Difficulty
☐2 Moderate Difficulty
☐1 Great Difficulty

e) Get out of bed by yourself

☐4 No Difficulty
☐3 Some Difficulty
☐2 Moderate Difficulty
☐1 Great Difficulty

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Attachment 5: Flu-PRO Questionnaire

This attachment provides a representative example of the Flu-PRO questionnaire that will be used in this study.

Participant ID: _____ **Participant Initials:** _____ **Date:** ____/_____/_____

Influenza Symptom Questionnaire

People experience the flu in different ways. We would like to know about the symptoms you have been experiencing during the past 24 hours. For each symptom, please mark one box ☐ under the response that best matches your experience. Mark the "Not at all" box, if you did not have that symptom in the past 24 hours.

What time is it? _____ **AM / PM (please circle)**

Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Runny or dripping nose	☐	☐	☐	☐	☐
Congested or stuffy nose	☐	☐	☐	☐	☐
Scratchy or itchy throat	☐	☐	☐	☐	☐
Sore or painful throat	☐	☐	☐	☐	☐
Swollen throat	☐	☐	☐	☐	☐
Difficulty swallowing	☐	☐	☐	☐	☐
Teary or watery eyes	☐	☐	☐	☐	☐
Sore or painful eyes	☐	☐	☐	☐	☐
Eyes sensitive to light	☐	☐	☐	☐	☐
Trouble breathing	☐	☐	☐	☐	☐
Chest congestion	☐	☐	☐	☐	☐
Chest tightness	☐	☐	☐	☐	☐
Dry or hacking cough	☐	☐	☐	☐	☐
Wet or loose cough	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐
Head congestion	☐	☐	☐	☐	☐
Sinus pressure	☐	☐	☐	☐	☐
Felt dizzy	☐	☐	☐	☐	☐
Felt lightheaded	☐	☐	☐	☐	☐

Monday, August 27, 2012, FLU-PRO Version 1.0

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Participant ID: _____ **Participant Initials:** _____ **Date:** ____/_____/_____

Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Lack of appetite (did not feel like eating)	☐	☐	☐	☐	☐
Felt nauseous (feeling like you wanted to throw-up)	☐	☐	☐	☐	☐
Stomach ache	☐	☐	☐	☐	☐
Sleeping more than usual	☐	☐	☐	☐	☐
Difficulty staying asleep	☐	☐	☐	☐	☐
Difficulty falling asleep	☐	☐	☐	☐	☐
Body aches or pains	☐	☐	☐	☐	☐
Weak or tired	☐	☐	☐	☐	☐
Chills or shivering	☐	☐	☐	☐	☐
Felt cold	☐	☐	☐	☐	☐
Felt hot	☐	☐	☐	☐	☐
Sweating	☐	☐	☐	☐	☐
Felt uncomfortable (general discomfort)	☐	☐	☐	☐	☐

In the past 24 hours, how often have you had any of the following symptoms?

	0 times	1 time	2 times	3 times	4 or more times
How many times did you vomit?	☐	☐	☐	☐	☐
How many times did you have diarrhea?	☐	☐	☐	☐	☐

	Never	Rarely	Sometimes	Often	Always
Sneezing	☐	☐	☐	☐	☐
Coughing	☐	☐	☐	☐	☐
Coughed up mucus or phlegm	☐	☐	☐	☐	☐

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Attachment 6: Additional Daily Diary Items to Flu-PRO

This attachment provides a representative example of the additional daily diary items to Flu-PRO that will be used in this study.

63623872FLZ2002 Additional daily diary items to Flu-PRO Version 1.0 dd 31JUL2015

Items to be asked in addition to the Flu-PRO.

1. Did you take any medication for your flu symptoms today?
   - ☐1 Yes
   - ☐0 No

2. Do you have asthma, COPD (chronic obstructive pulmonary disease) or both?
   - ☐1 Yes
   - ☐0 No

3. [Only asked if answer to the question above is "yes"]. Did you use any rescue medication today for your asthma or COPD?
   - ☐1 Yes
   - ☐0 No

4. Overall, how severe were your flu symptoms today?
   - ☐0 No flu symptoms today
   - ☐1 Mild
   - ☐2 Moderate
   - ☐3 Severe
   - ☐4 Very severe

5. Overall, how were your flu symptoms today compared to yesterday?
   - ☐1 Much better
   - ☐2 Somewhat better
   - ☐3 A little better
   - ☐4 About the same
   - ☐5 A little worse
   - ☐6 Somewhat worse
   - ☐7 Much worse

6. How much did your flu symptoms interfere with your usual activities today?
   - ☐1 Not at all
   - ☐2 A little bit
   - ☐3 Somewhat
   - ☐4 Quite a bit
   - ☐5 Very much

7. Have you returned to your usual activities today?
   - ☐1 Yes
   - ☐0 No

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8. In general, how would you rate your physical health today?
   - ☐5 Excellent
   - ☐4 Very Good
   - ☐3 Good
   - ☐2 Fair
   - ☐1 Poor

9. Have you returned to your usual health today?
   - ☐1 Yes
   - ☐0 No

Attachment 7: Cardiovascular Safety - Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	HR	PR	QRS	$QT_{corrected}$
Abnormalities on actual values				
Abnormally low	< 45 bpm	< 110 ms	-	-
Abnormally high	≥ 120 bpm	> 220 ms	≥ 120 ms	-
Borderline prolonged QT (males)	-	-	-	450 ms < QTc ≤ 480 ms
Borderline prolonged QT (females)	-	-	-	470 ms < QTc ≤ 480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤ 500 ms
Pathologically prolonged QT	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc < 30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤ 60 ms
Abnormally high QTc change	-	-	-	ΔQTc > 60 ms

For absolute QTc parameters the categories are defined based on the ICH E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	DBP	SBP
Abnormalities on actual values			
Abnormally low	< 45 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥ 100 mmHg - < 110 mmHg	≥ 160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.
[b] The classification of AEs related to hypotension and hypertension will be done according to the WHO grading scale (see also Attachment 1).

INVESTIGATOR AGREEMENT

I have read this document and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the document and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Lorant Leopold

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE