Statistical Analysis Plan

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

JNJ-63623872

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Abbreviations

AE	Adverse event
AUC	area under the curve
AUC_{24h}	area under the plasma concentration-time curve from time 0 to 24 hours
bid	bis in die; twice daily
BMI	body mass index
C0h	predose plasma concentration
CI	confidence interval
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CPAP	Clinical Pharmacology Analysis Plan
CTP	clinical trial protocol
CV	coefficient of variation
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
FAS	Full Analysis Set
GMR	geometric mean ratio
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
ITT	Intent-To-Treat
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PT	preferred term
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RNA	Ribonucleic Acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SI	international system

Amendments

Amendment 1

Changes compared to SAP version 1.0, dated 15 March 2017:

Rationale: The original analysis of viral load qRT PCR assumed that both the limit of detection (LOD) and quantification (LOQ) were the same (2.18 log10 vp/mL). As this has been changed to two different limits: LOD of 2.05 log10 vp/mL and LOQ of 2.18 log10 vp/mL, the analysis description had to be updated accordingly.

Updates were made to Sections 3.2 (Analysis sets) and 4.2.2 (Viral Kinetics).

1. Study description

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of efficacy and safety of the investigational compound JNJ-63623872. The SAP is to be interpreted in conjunction with the protocol. A detailed analysis plan for the pharmacokinetic data will be described in a Clinical Pharmacology Analysis Plan (CPAP). The Clinical Pharmacology Analysis Plan will include the primary endpoint and all secondary and exploratory endpoints related to PK and PK/PD for this study.

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.

1.1. Study objectives

Please note this SAP does not cover the primary objective and the exploratory PK/PD relationship (efficacy and safety). These objectives will be analyzed and reported separately according to the clinical pharmacology analysis plan (CPAP).

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:

- Safety and tolerability.
- 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.
- Viral load over time and rate of decline in viral load during treatment as measured by qRT-PCR and/or viral culture.
- Area under the curve (AUC) of viral load as measured by qRT-PCR and/or viral culture.
- 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).

- Change in duration and severity of clinical symptoms as measured by the Flu-PRO.
- Time to improvement of vital signs.
- Time to improvement of respiratory status.
- Improvement on the ordinal scale.
- Emergence of drug resistance as detected by genotype and/or phenotype.
- Time to return to premorbid functional status (time to return to usual activities).
- 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:

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

1.2. 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.

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.

1.3. Study population

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

The inclusion and exclusion criteria for enrolling subjects in this study are described in section 4 of the Protocol. If there is a question about the inclusion or exclusion criteria, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

1.4. Sample Size Justification

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 1. Based on those data a between-subjects CV of 60% was assumed as a reasonably conservative estimate for the current study.

Table 1: 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 Cmin 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 Cmin, 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 2 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)

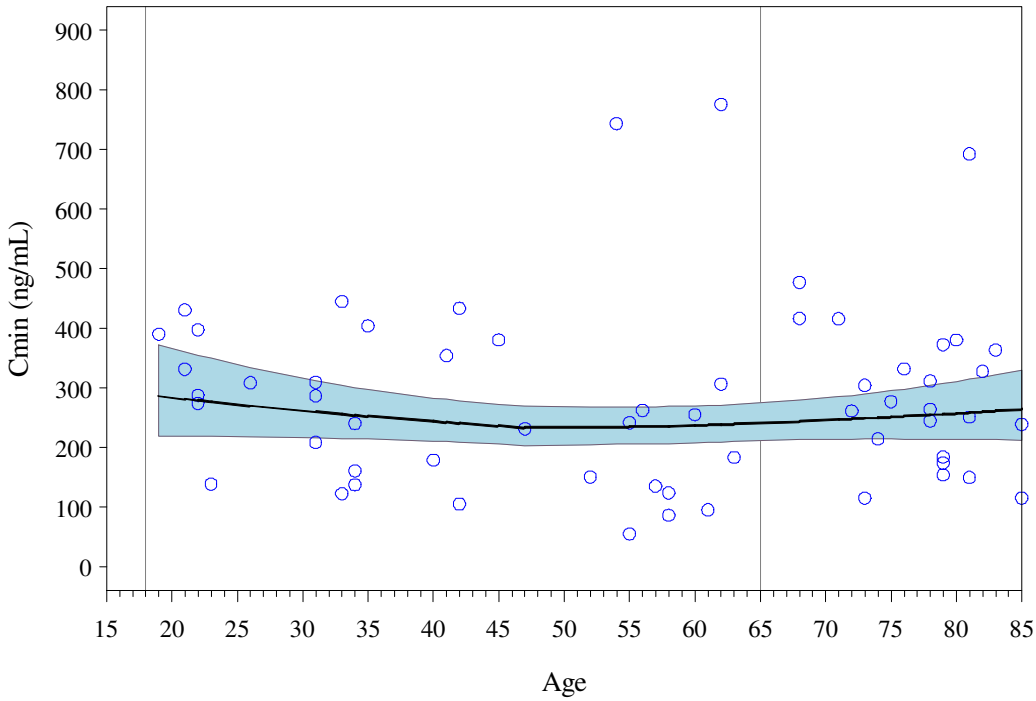


Table 2: Precision of the LOESS Confidence Band Around the Prediction

Cmin (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 3 presents the one-sided upper confidence limits for a range of numbers of treated subjects.

Table 3: 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 4 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 4: 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.

1.5. Randomization and Blinding

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.

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.

1.6. Changes to the planned analysis, not specified by protocol amendments before DB lock

The protocol defines the improvement of vital signs using symptoms for temperature, blood oxygen saturation, heart rate, SBP and respiration rate. In the resolution criterion for temperature the protocol defines rectal and tympanic temperatures. However, only oral temperatures are measured in the 63623872FLZ2002 trial. Additionally the trial is stratified based on age categories for adults and elderly patients. It is known that older subjects have lower mean oral body temperatures. Taking these aspects into account the resolution criterion for temperature has been adapted to using oral temperature ≤ 36.5 °C for elderly and ≤ 37.2 °C for adults instead of rectal or tympanic temperature ≤ 37.2 °C or ≤ 37.8 °C respectively as specified in the protocol.

2. Interim and Final analysis

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.

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.

An interim analysis may be performed to support regulatory activities. In that case the same Statistical Analysis Plan (SAP) will be used for the interim and the final analysis.

Should an interim analysis be performed this analysis will be based on the number of subjects randomized up to that timepoint. The interim analysis will be performed by a statistical support group independent of the study biostatistician team and any personnel directly involved in the conduct of the study. More details about their formation, roles, responsibilities and the level of unblinding of the different parties, can be found in the Interim Analysis Committee Charter (IAC Charter).

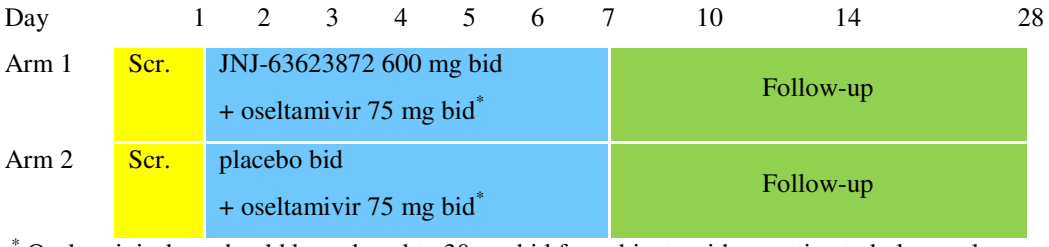
3. General analysis specifications

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.2.

3.1. Visit Windows, Phase Definitions and Baseline

The study is set up as shown in Figure 2. The phases will be constructed as shown in Table 5.

Figure 2: Study time line.



* 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.

3.1.1. Phase Definitions

Table 5: Construction of phases

Trial phase	Trial sub period[*1]	Start date	End date
Screening (phase 1)		The date of signing the informed consent with 00:00 as a timepart	1 minute before the first study medication intake
Treatment (phase 2)		Datetime of first study medication intake	Datetime of last investigational medication intake[*5] + 24 hours
	Hospitalization (sub period 1)[*2]	In case first intake of study medication occurred at the hospital[*4]: Datetime of first study medication intake	The minimum of: • The last date of discharge from hospital[*4] + timepart 23:59 • The Datetime of last investigational medication intake[*5] + 24 hours
	Outpatient (sub period 2)[*3]	In case first intake of study medication did not occur at the hospital[*4]: Datetime of first study medication intake In case first intake of study medication occurred at the hospital[*4] and last discharge from the hospital occurred before the end of the treatment	Datetime of last investigational medication intake[*5] + 24 hours

Trial phase	Trial sub period[*1]	Start date	End date
		phase: End date hospitalization phase[*4] + 1 minute	
Follow-up (phase 3)		End of the treatment phase +1 minute	Trial termination date (date of last contact) or cut-off date for the Interim analysis, whichever comes first with 23:59 as a timepart

[*1]: A treatment period will be constructed in the derived datasets with the same start and end date as the treatment phase.
[*2]: The hospitalization phase will not be made for subjects that took the first intake of study medication at home.
[*3]: The Outpatient phase will not be made for subjects that are still in hospital at the end date of the treatment phase
[*4]: the start date and end date of hospitalization will be derived from the eCRF Hospitalization page. If the start date is not available, the start date of hospitalization will be the date of first treatment (as being hospitalized is an inclusion criterion in the protocol). If the end date is not available the date will be derived from the subject exposure domain as the last visit that is not 'Outpatient' (in case no outpatient visit available in the exposure domain, the subject is assumed to be hospitalized during the entire treatment phase). Should a subject be discharged and again hospitalized during the treatment phase, the entire period will be regarded in the hospitalization phase.
[*5]: In case the time part of the last medication intake is missing the imputed time part will be used

In case the time part of first medication intake is missing and visit time point is available, the time will be imputed with 8:00 if the first medication was taken in the morning or with 20:00 if the first medication was taken in the evening. In case the time of the last medication intake is missing, the time part will be imputed with 8:00 if the last medication was taken in the morning or with 20:00 if the last medication was taken in the evening

The last phase, whichever it is for a subject, always ends on 23:59 of the day of trial termination (last contact) or the cut-off date in case the data are analyzed for an interim analysis (whichever comes first).

For phase allocation of trial termination, 23:59 will be used as time of trial termination (on the trial termination date) in the allocation rule.

Assessments will be assigned to phases based on their date time, but seconds will be ignored overall. If the day part of the start date of the assessment is present but the time part is missing, the assessment will be treated as if it happened at 0:00 of the day of the assessment (except for Adverse Events see details in section 4.3.1). If the day part of the end date of the assessment is present but the time part is missing, the assessment will be treated as if it happened at 23:59 of the day of the assessment.

The number of days in the study (reldy) will be defined as:

$$reldy = visit\ day - reference\ day + 1$$

for visits on or after the reference day, and

$$reldy = visit\ day - reference\ day$$

for visits before the reference, where the reference day equals the date of first study medication intake.

3.1.2. *Use of Unscheduled Assessments*

All scheduled assessments after first administration of trial medication will be used. Unscheduled assessments will not be used in descriptive statistics or any per-time point analysis, but will be shown in listings as applicable. Pre-dose unscheduled assessments will be taken into account for baseline determination and post dose unscheduled assessments will be taken into account for worst-case determination.

3.1.3. *Analysis visits*

In general, AVISIT will be derived as the day of a scheduled visit, assessment or self-assessment (e.g. 'Day 4'). AVISITN will be the numeric counterpart (e.g. for 'Day 4' AVISITN will be 4). The AVISIT for scheduled measurements before first intake will be set to 'Screening' with AVISITN = -1.

For the PRO post-baseline assessments of the FLU-iiQ™ and FLU-PRO questionnaires, AVISIT and AVISITN will be derived from the number of days in the study relative to the start of study treatment (reldy). Post-baseline assessments taken from 00:00 until 03:00 will be assigned to the day before (e.g. a recording on day 4 at 01:00 will be assigned AVISIT= Day 3).

3.1.4. *Analysis timepoints*

In general, for parameters that were assessed more than once daily, the analysis time point (ATPT) will the time point as reported in the database.

For the PRO assessments of the FLU-iiQ™, all post-baseline records from day 1, 03:01 until day 15, 03:00 will be assigned to an analysis time point (ATPT) using the following windows: morning = from 3:01 until 15:00 and evening = from 15:01 until 03:00. The measurements taken from 00:00 until 03:00 will be assigned to the evening of the day before (e.g. a recording on day 4 at 01:00 will be assigned AVISIT= Day 3, ATPT=Evening). For all records from day 15, 03:01 until the final study visit/Safety follow-up visit the analysis time point is the analysis visit.

3.1.5. *Use of records in case more than 1 record per analysis visit/time point*

PRO assessments of FLU-iiQ™ and FLU-PRO:

- Questionnaires that have too many missing items (> 50% or for the FLU-PRO see Minimal data requirement rules) will not be used in the anlysis. This will also be applied for the determining the baseline questionnaire.
- For derivation of FLU-iiQ™ composite symptom score, composite impact scores (modules 2-4) and total composite impact score; FLU-PRO domain scores (6 domains) and FLU-PRO total score:

  If two or more records, for which a compostie, total or domain score can be calculated, are available within an analysis visit/analysis time point, only the records from the worst questionnaire[1] will be used for the analyses. The worst

questionnaire is the questionnaire with the highest score on an individual item. If 2 or more questionnaires have the same highest score on an individual item, the one with the highest average score over all items will be used (ignoring missing items). If two or more questionnaires also have the same average score, the one which came last in time will be used.

[1]A "questionnaire" is the combination of 7 symptom items for the FLU-iiQ™ composite symptom score; 6, 4 and 5 items for composite impact scores of module 2, module 3 and module 4 respectively and all 15 impact score items for the total composite impact score. Similarly, for FLU-PRO a questionnaire is the combination of the items needed to calculate the 6 different FLU-PRO domains scores and all 32 items of FLU-PRO for the total FLU-PRO score.

- For the analysis of the additional questions of the FLU-iiQ™ and FLU-PRO, if two or more records are available within an analysis visit/time point, the record to be used will be determined per individual question. Per question, only the record with the worst[1] result will be used for the tabulations. If the 2 or more records have the same worst result, the one which came last in time will be used.

[1]"Worst" is defined as the lowest score for the FLU-iiQ™ additional questions and for FLU-PRO additional questions 7, 8 and 9. "Worst" is defined as the highest score for FLU-PRO additional questions 1-6.

3.1.6. Baseline Definitions

In general, the baseline record is defined as the last record before the first intake of the study drug. (For programming purposes the last record before intake will be doubled in the ADAM datasets, the doubled record will be renamed with AVISIT = 'Baseline', AVISITN = 0 and will be assigned to the treatment phase.)

For the FLU-iiQ™ and FLU-PRO questionnaire assessments, if a baseline record is not available, the baseline record is defined as the first available assessment within 2 hours after first intake of study drug.

3.2. Analysis sets

Population of the analyses covered by this SAP will be:

- *Randomized Analysis Set (RAND):* All randomized subjects with a randomization date at or before the date of first intake of medication, or with a randomization date and no medication intake.
- *Randomized and/or Treated Analysis Set (RT):* All randomized subjects and/or all subjects who received at least 1 dose of study drug.
- *Safety Set or All Subjects Treated (AST):* All subjects who received at least 1 dose of study drug, analyzed as treated.
- *Full Analysis Set (FAS):* All randomly assigned subjects who receive at least 1 dose of study drug and who have a confirmed infection with influenza A. Confirmation of Influenza A will be obtained from virology data. If there are no virology data available at cut-off of the interim analysis, then a subject will be considered infected with Influenza A and included in the FA set. If there are no virology data available at final analysis, then a subject will be excluded from the FA set. Analyses on the Full Analysis Set will be analyzed as treated.

A subject is considered to have a confirmed infection with influenza A if he/she has:

- at least one positive PCR result from central lab testing[1] (lbtestcd = 'INFAVLD') at baseline or pre-baseline;

  else

- at least two positive PCR results from central lab testing[1] (lbtestcd = 'INFAVLD') post-baseline;

  else

- at least one positive PCR result from central lab testing[1] (lbtestcd = 'INFAVLD') post-baseline and one positive PCR result from local lab testing (lbtestcd = 'INFVSCR') post-baseline, provided that both are from a separate visit day;

  else

- at least one positive PCR result from local lab testing (lbtestcd = 'INFVSCR') at baseline or pre-baseline, provided that no central lab testing is available at baseline or pre-baseline.

  else

- at least two positive PCR results from local lab testing (lbtestcd = 'INFVSCR') post-baseline, provided that no central, or local lab testing is available at baseline or pre-baseline, and no central lab testing is available post-baseline.

[1]Viral load results from central lab testing (lbtestcd = 'INFAVLD') recorded as 'TARGET NOT DETECTED' will be considered as negative, all other results ('<2.18' and numeric results) as positive.

The Randomized and/or Treated Analysis Set (RT) will be used in all listings. The Safety Set (AST) will be used to perform the evaluation of all safety variables. The Full Analysis Set (FAS) will be used to perform the evaluation of all efficacy variables.

3.3. Definition of Subgroups

The following two age categories (>=18 - <65 years, >= 65 - <= 85 years) are strata in the study and will also be used as subgroups for the subject information, safety and the efficacy analyses.

For demographics, baseline disease characteristics andvirology the influenza subtype category (A/H1N1, A/H3N2 and Other) will be used as subgroup.

3.4. Statistical Methods

This SAP covers the statistical analysis for Interim and Final analyses. Details of the single displays are described in the Data Presentation Specifications (DPS).

- The analysis population will be indicated in the titles of the displays.

- The footnote of the displays for the interim analysis will report the cut-off date of the data snapshot or the locked database that have been used for the analysis.
- All results will be presented per treatment group. Tables on subject disposition, exposure, demographic data and baseline disease characteristics will include a 'Total' treatment group, pooling all subjects.
- Tables, listings and figures will be made by age category (stratum) and overall.
- Listings will be presented by treatment group and ordered by subject number and time point (if applicable).
- All outputs should be self-explanatory and therefore appropriate footnotes will be provided to clarify the contents of each listing, table or graph.
- In case the X-axis of a graph shows a time component, the distances between the time points will be proportional (not equidistant). Furthermore, when statistics are joined over time by a line, the actual statistics will be depicted by means of a symbol.
- Unless specified otherwise, continuous parameters will be summarized using the following statistics: number of observations, mean, standard deviation, minimum, median and maximum. The mean and median will be presented with one decimal place, while the standard deviation with two decimal places more than the decimal places of the raw data. The minimum and maximum will be presented to the same number of decimal places as the raw data.

4. Analyses

4.1. Subject Information

All general analyses will be done on the Full Analysis Set and the Safety Set unless specified otherwise for a specific display.

4.1.1. Subject disposition

Summaries will be provided for the following disposition information:

- Number of subjects screened, screening failures, not randomized, randomized set, randomized and not treated, randomized and/or treated, safety set, treated but not Influenza A and full analysis set
- Number of subjects who completed/discontinued treatment and/or the trial, with the reasons of discontinuation.
- Number of subjects with a visit at each scheduled analysis time point by phase.

4.1.2. Summaries will be made overall and by age category, by treatment group (and overall).Demographics parameters and baseline disease characteristics

All demographics and baseline disease characteristics will be summarized overall and by age category, by treatment group (and overall); and by influenza subtype category, by treatment group (and overall) Descriptive statistics or frequency tabulation will be provided for the following parameters.

- Demographic parameters:
  - Sex (Male, Female)
  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other). The specification of the category 'Other' will only be listed.
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Country
  - Geographic region (based on country: North America (to include Puerto Rico), Europe, Asia-Pacific, South America)
  - Age (years and categories: >=18 - <65 years, >= 65 - <= 85 years)
  - Weight at baseline (kg)
  - Height at baseline (cm)
  - BMI at baseline = Weight at baseline (kg) / (Height at baseline (m))^2 (rounded to 1 decimal. Although available in the raw data, BMI will be recalculated from last weight and height measurement before start of treatment)
  - Site ID

- Tobacco use: cigarettes, cigars, patches/gum, pipes, smokeless tobacco (Yes, No: including ex-smokers)
- Childbearing Potential (only listed)

- Baseline disease characteristics:
  - Influenza subtype category (A/H1N1, A/H3N2, other)
  - Baseline influenza A viral load (log10 copies/mL), assessed by qRT-PCR
  - Baseline influenza A viral titer (log10 TCID50/mL) assessed by viral culture
  - Composite symptom score of the seven primary influenza symptoms at baseline from the FLU-iiQ^{TM} (as defined in section 4.2.3)
  - Baseline FLU-PRO total score (as defined in section 4.2.6)
  - NEW Score at baseline
  - Respiration rate at baseline
  - Arterial oxygen saturation at baseline
  - Supplemental oxygen at baseline (Yes, No)
  - Oral temperature (°C) at baseline
  - Systolic blood pressure at baseline
  - Heart rate at baseline
  - Level of consciousness at baseline

4.1.3. Prior and Concomitant Medications

Medications taken up to 7 days before first dose of study drug and up to the Final Study Visit/Safety Follow-up Visit will be summarized by preferred term using the World Health Organization-Drug Dictionary for the FA Set and the Safety Set as frequency tables in 2 parts:

1. Prior medication: medication that started before the first dose of study drug, regardless of when dosing of the medication ended
2. Concomitant medication: medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date.

(Medication that started before the first dose of study drug and continued after the first dose of study drug will be summarized as prior medication and separately as concomitant medication.)

A frequency tabulation of concomitant medication will be shown by ATC class level up to level 3. Frequency tabulations will be made for concomitant antibiotics and corticosteroids by ATC class and by hospitalization status (Yes/No). Tabulations of concomitant corticosteroids and antibiotics administered

because of adverse events reported as influenza complications will also be made. Separate frequency tabulations will be made for antipyretic medication and oxygen supplementation. Antipyretic medication will be categorized as Paracetamol, Ibuprofen, or other. The table showing oxygen supplementation will be tabulated per analysis visit and phase.

All tabulations will be created overall and by age group, by treatment group (and overall).

If a prior/concomitant therapy record misses components of its start and/or stop dates (time and/or day and/or month and/or year), the following actions will be taken:

1. In case of partial start or stop date/times, the concomitant therapy records will be allocated to prior and/or concomitant using the available partial information, without imputations.
2. In case of a completely missing start date, the prior and/or concomitant therapy will be considered as having started before the trial.
3. In case of a completely missing end date, the prior and/or concomitant therapy will be considered as ongoing at the end of the trial.

4.1.4. Medical history

Medical history will only be listed.

The influenza vaccination status will be tabulated by previous season, current season and both previous and current season (for subjects who got vaccinated in both seasons), overall and by age category, by treatment group (and overall).

The use of antiviral influenza medication prior to hospitalization will be tabulated separately, overall and by age category, by treatment group (and overall).

Influenza history will be listed, including information on first acute respiratory symptoms, influenza vaccination and previous antiviral influenza therapy. Pre-treatment Influenza complications will also be listed.

4.1.5. Treatment Exposure and Compliance

The treatment duration is defined as date/time of last study drug intake – date/time of first study drug intake + 12 hours.

Note: treatment interruptions will not be taken into account for the above definition.

Dosing compliance is calculated as the actual number of doses taken, as a percentage of the planned number of doses. The actual number of doses taken will be derived from the exposure information (EX domain) during hospitalization and from the drug accountability information (DA domain) after discharge from hospital.

In the exposure information the amount of medication administered during hospitalization is given per visit and time point, the actual number of tablets/capsules during hospitalization is the sum of this amount per medication for the records that are not outpatient records.

The actual amount of tablets/capsules taken after discharge will be derived from the drug accountability information as the difference between the drug dispensation at discharge and the returned amount (in case both amounts are known).

The actual number of doses taken during the study is the sum of the actual number of medication taken during hospitalization and after discharge, for Placebo or JNJ872 this number needs to be divided by 2 as the study uses 300 mg tablets. In total, the planned number of medication is 28 tablets of Placebo or JNJ872 and 14 capsules of Oseltamivir. Hence the planned number of doses per medication equals 14 doses.

Actual treatment duration and dosing compliance will be summarized descriptively overall and by age category, by treatment group (and overall).

4.2. Efficacy

All efficacy analyses will be done on the full analysis set. Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment group and by stratum age category (>=18 - <65 years, >= 65 - <= 85 years, overall). Derived parameters will also be listed. No formal statistical hypothesis testing will be performed.

4.2.1. Clinical Outcomes

- **Incidence of influenza complications**
  The incidence of influenza complications from first intake up to Day 28 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 occurrence (yes/no) of influenza complications from first intake up to Day 28 of each (sub) category will be analyzed using logistic regression with treatment group as covariate. In case influenza complications occur in both age categories, age category will also be added as a covariate and as an interaction with treatment group. If the model will not fit the age category and it's interaction will be removed. Odds ratios and associated 95% CIs will be reported of active vs. control treatment and – if available – of elderly patients vs. patients <65 years.

- **Time to improvement of vital signs**

The time to improvement of vital signs is defined as the time (in hours) from first study treatment until the first assessment (actual date and time) of a successive series of 3 recordings (over 4 scheduled successive analysis time points, 1 missing time point is allowed) where at least 4 of 5 symptoms (temperature, blood oxygen saturation, heart rate, SBP, respiration rate) are recovered, with at least 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.

Only vital signs assessments assessed during hospitalization and up to Day 14 (during hospitalization) will be taken into account to determine time to improvement of vital signs. Assessments taken after hospital discharge or after day 14, whichever, comes first will not be taken into account. In case, there was more than one hospitalization period, only assessments of the first hospitalization period will be used.

In cases where there are no sufficient recordings of clinical stability as defined above, the endpoint will be censored. Censoring will be at the first time of clinical stability, if and only if after this observation there is no recording of non-resolved influenza symptoms (ignoring missing recordings). If there are no recordings of resolved symptoms satisfying this criterion, the time of censoring is the first possible time point an assessment could have been done after the last observation of vital signs recordings, which is 13:00 on the same day if the last observation was a morning assessment (from 3:01 until 11:00), 21:00 if the last observation was an afternoon assessment (from 11:01 until 19:00), 5:00 the next day if the last assessment was an evening assessment (from 19:01 until 03:00). There are two exceptions: in case the last available vital signs record is on the day of discharge in the evening or on day 14 during hospitalization in the evening. If at this record (last record for the subject to be taken into account for time to clinical stability) there is no clinical stability, the time of the last assessment (day of discharge, evening or day 14, evening) will be taken as the time of censoring.

The data will be presented using a Kaplan-Meier curve and Kaplan-Meier estimates by treatment group, overall and by age group.The time to event data will be modeled using the accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. Age category, NEW Score at baseline and treatment group will be included as covariatesIf the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and the Gehan-Wilcoxon method.

Table 6: Resolution Criteria for Vital Signs

Assessment	Resolution Criterion
Temperature	Oral temperature ≤ 36.5 °C for elderly and ≤ 37.2 °C for adults
Oxygen saturation	≥ 92% on room air without supplemental oxygen*
Respiration rate	≤ 24/min
Heart rate	≤ 100/min
Systolic blood pressure	≥ 90 mmHg

*On room air to be obtained from "Was oxygen saturation measured on room air?" on Vital Signs pages (SUPPVS.QVAL for SUPPVS.QNAM = 'VSOXSMRA'

- **Time to improvement of respiratory status**
  Time to improvement of respiratory status is defined as the time (in hours) from first study treatment until the first assessment (actual date and time) of a successive series of 3 recordings (over 4 scheduled successive analysis time points, 1 missing time point is allowed) where normalization of blood oxygen saturation and respiration rate occurred (as defined in Table 6). Analysis performed will be analogous to the analysis for the time to improvement of vital signs. Note that the NEW Score at baseline should not be added as covariate in the models.

- **Clinical outcome on day 8**
  The ordinal scale consists of 6 categories that are exhaustive, mutually exclusive, and ordered (Table 7). For all patients, the category at days 1 to 15 will be established as the worst category on that day. The clinical outcome on day 8 will be further analyzed.

  The analysis of the clinical outcome on day 8 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. Age category (>=18 - <65 years, >= 65 - <= 85 years) and baseline clinical outcome category will be added to the model. In case the model will not fit, age category and subsequently baseline category will be deleted.

  In case of missing data (>10%), multiple imputation under the missing-at-random assumption will be employed as a sensitivity analysis. The Markov chain Monte Carlo (MCMC) method will be used to create a number of multiple imputation datasets with monotone missingness in the clinical outcomes (baseline until day 15). The number of imputation datasets will be the same as the percentage of missing data (White *et al*. 2011). A monotone ordinal logistic regression imputation model will be used to complete the remaining missing clinical outcomes. The models fitted using the multiple imputation datasets will be the same as the final model on the actual data. The results from the models on the multiple imputation datasets will be combined taking into account the between and within variation of the results.

  Additionally a Wilcoxon–Mann–Whitney test will be performed to compare the clinical outcome on day 8 between the two treatments.

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

4.2.2. Viral Kinetics

Influenza viral load and viral titer will be determined and quantified in Nasal MT swab samples taken daily until discharge or until Day 14, whichever comes first. When subjects are discharged from the hospital and still positive for influenza A virus, they are encouraged to perform self-swabbing at home if practically feasible. All swabs will be analyzed using quantitative real time polymerase chain reaction (qRT-PCR) and/or viral culture ($TCID_{50}$) and/or PCR-based rapid molecular testing (if applicable).

All analyses described below, will be done on the qRT-PCR and viral culture results from central lab testing. As a sensitivity analysis, time to viral negativity will also be evaluated on a combination of the qRT-PCR results from central testing with the local rapid influenza test results (at home or on site) of days on which the results from central lab testing were missing.

The viral culture ($TCID_{50}$) measurements are analyzed using two methods (depending on influenza subtype); i.e. NP ELISA and Hemagglutination Inhibition Assay. For analysis purposes the results from the NP ELISA method will be used when available, otherwise the results from the Hemagglutination Inhibition Assay will be used. This will be determined per time point. As a consequence the results of a subject can be a combination of both methods (for example at baseline the NP ELISA result is used and at day 4 the Hemagglutination Inhibition Assay result is used).

Viral load results recorded as 'TARGET NOT DETECTED' will be considered as negative, all other results ('<2.18' and numeric results) as positive. Viral titer results recorded as '<0.75' will be considered as negative, all other results as positive.

For analysis purposes the log10 qRT-PCR viral load will be imputed with 2.12 when the result is '<2.18' (i.e. below limit of quantification) and with 0 if result is 'TARGET NOT DETECTED' (i.e. below limit of detection: <2.05). The log10 $TCID_{50}$ viral titer will be imputed with 0.375 when the result is '<0.750'.

- **Viral load and viral titer actual values and change from baseline**

  Descriptive statistics and mean (SE) plots will be shown for the log10 values of viral load and viral titer (qRT-PCR and viral culture) and the changes from baseline calculated in log10 (vp/mL or $TCID_{50}$/mL).

- **Incidence of influenza A viral negativity by assessment**
  The proportion of subjects with a negative viral load and a negative viral titer will be tabulated at each time point.In addition, per parameter and time point a logistic model with baseline viral load/viral titer and age category (>=18 - <65 years, >= 65 - <= 85 years) as covariates will be used to obtain the odds ratios (95% CI) for the comparison of the incidence of influenza A viral negativity of treatment versus placebo.

  Stacked barcharts of the percentage of subjects per response category will be made by day and treatment for viral load and viral titer. The following response categories will be used:

  - For viral load (log10 vp/mL) measurements:
    - Target not detected (<2.05 log10 vp/mL)

- Target detected (<2.18 log10 vp/mL)
- Quantifiable (≥2.18 log10 vp/mL)

➢ For viral titer (log10 $TCID_{50}$/mL) measurements:

- Negative (<0.75 log10 $TCID_{50}$/mL)
- Positive (≥0.75 log10 $TCID_{50}$/mL)

- **Time to influenza A viral negativity**

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 confirmed negative nasal MT swab was recorded (in days) i.e. defined as time in days from start of treatment to first of assessments ='negative' and the next assessed measurement is not ='positive'(ignoring missings, i.e. if first 'negative' is last available assessment or if next assessed result after first 'negative' is also 'negative'). If this doesn't occur, a subject will be censored at the time of the last observed nonnegative swab + 1 day. Note that at baseline every subject is considered positive.

This will be done separately for viral load and viral titer assessments from central lab testing. As a sensitivity analysis, time to negativity will also be evaluated on a combination of qRT-PCR results from central lab testing and rapid influenza test results (from self or on site swabs). The available central lab qRT-PCR results (qualitative) will be complemented with the results of the rapid influenza tests that are available on days where central lab testing results are not available.

The time to influenza A viral negativity will be presented using Kaplan-Meier curves and Kaplan-Meier estimates by treatment group, overall and by age group. For a comparison between treatment arms, the time to influenza A viral negativity will be analyzed using an accelerated failure time model. The accelerated failure time model will use a Weibull, log-logistic, lognormal or gamma distribution based on goodness of fit criteria (AIC). As covariates the baseline viral load and the age category (>=18 - <65 years, >= 65 - <= 85 years) will be included. If the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

- **Viral AUC calculated from baseline to Day 8**

The viral AUC, calculated separately for viral load and viral titer, from baseline to Day 8 will be estimated for each treatment arm using a mixed model for repeated measurements, i.e., the AUC will not be calculated for each subject and then analyzed, but the AUC will be calculated for each treatment arm using log10 transformed viral load data over time of each subject. This approach ensures an optimal approach towards missing data.

Baseline and post-baseline mean viral load values over time (at time points Day 1 to 5 and Day 8) will be analyzed using a restricted maximum likelihood based repeated measures approach using a constrained longitudinal data analysis. The analysis model will include the fixed, categorical effects of visit, treatment-by-visit interaction, age category-by-visit interaction and treatment-by-visit-by age category interaction. The following list of covariance structures will be applied in the model fit, in the specified order, and the first correlation structure to yield convergence will be applied in the analysis:

- Unstructured [UN]
- Ante-dependence [ANTE(1)]
- Heterogenous Toeplitz [TOEPH]
- Heterogeneous CS [CSH]
- Heterogeneous AR(1) [ARH(1)]
- Toeplitz [TOEP]

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The area under the viral load curve (viral AUC) will be based on the Full Analysis set. The model estimates from the model above will be used to estimate the viral AUC for each treatment and to derive the difference in the viral AUCs for active versus placebo, overall and by age category.

A mean ±95% CI plot will also be provided for the estimated viral load and estimated viral titer over time.

- **Rate of decline of viral load and viral titer**
  The rate of decline in quantitative viral load (log10 vp/mL per day) and quantitative viral titer (log10 TCID50/mL per day) will be estimated per treatment through a linear mixed model with repeated measures. Treatment and age group will be added as categorical effects, time will be added as a continuous covariate and the interactions between treatment and time, age group and treatment, and age group and time will also be added. The model will be fit with a random intercept and a random slope. In case the model will not fit, age category and interaction terms with age group will be deleted.

- **Peak viral load and peak viral titer**
  The peak viral load/viral titer is defined as the highest value of viral load/viral titer during treatment and follow-up (including the baseline value) calculated as log10 (vp/mL or $TCID_{50}$/mL). For the peak viral load/ viral titer a geometric mean ratio (GMR) will be derived using a general linear model including treatment group, age category and the interaction of both. Descriptive statistics will be provided by treatment group, overall and by age group.

4.2.3. Influenza Symptom Score (FLU-iiQ™ Module 1)

The influenza symptom score (Flu-iiQ™ Modules 1) will be assessed 2 times a day, from study entry (Baseline, Day 1) through Day 14, and once daily from Days 15 through Day 28 (Safety Follow-up Visit).

- **Composite symptom score**
  The subject's composite symptom score per datetime is defined as the mean of the corresponding non-missing 7 primary influenza symptoms of the Flu-iiQ™ (cough, sore throat, headache, nasal congestion, feeling feverish, body aches or pains, and fatigue (tiredness)) on a 0-3 scale calculated for each datetime the questionnaire was filled. For each time point a change from baseline will be calculated.

  An alternative composite symptom score will be calculated using all 10 influenza symptoms included in Module 1 of the Flu-iiQ™ instrument.

  If more than 50% of the items to construct a Composite symptom score are missing, the value for that composite score is coded as missing (i.e. 4 or more items missing for the primary symptom composite score and 6 or more items missing for the composite score based on all 10 items).

  The actual composite symptom scores and changes from baseline will be shown descriptively and by mean (SE) plots per analysis timepoint.

- **Daily average symptom score**
  For the Flu-iiQ™ a daily average symptom score will be derived averaging the composite symptom scores (based on 7 primary and all 10 items respectively) per day over all post-baseline analysis timepoints. Also a total average symptom score over the daily averages of the composite symptom score will be calculated. The baseline value of the daily average symptom score will be the baseline score of the respective individual influenza symptom score or the composite symptom score..

  The daily averages of the composite symptom scores will be shown descriptively and by mean (SE) plots. The total average composite symptom score will be shown descriptively.

- **Time to Resolution of Influenza**
  Resolution of influenza symptoms is defined as the first of a successive series of 2 recordings in which all symptom scores for each of the 2 assessments are 0 or 1 for all 7 primary influenza symptoms of the Flu-iiQ™ (cough, sore throat, headache, nasal congestion, feeling feverish, body aches or pains, and fatigue (tiredness)). If the first record of a successive series of 2 recordings of resolved influenza is before day 14 in the evening then the 2 successive recording should have been done over 3 scheduled successive analysis timepoints, 1 missing timepoint is allowed. If the first record of a successive series of 2 recordings of resolved influenza is at or after the evening record of Day 14 then the 2 successive recordings should have been done within 2 scheduled successive analysis timepoints (no missing allowed).

  In cases where there are no sufficient recordings of resolved influenza as defined above, the endpoint will be censored. Censoring will be at the first

time of resolved influenza symptoms, if and only if after this observation there is no recording of non-resolved influenza symptoms (ignoring missing recordings). If there are no recordings of resolved symptoms satisfying this criterion, the time of censoring is the first possible time point a diary entry could have been made after the last observation of the presence of influenza, which is 20:00 on the same day if the last observation was a morning diary entry (from 3:01 until 15:00), 8:00 the next day if the last entry was an evening diary (from 15:01 until 03:00) (Day 1 until Day 14, morning). If the last observation of the presence of influenza is on Day 14 in the evening or after day 14 then the time of censoring is the time of the last diary entry + 24 hours. One exception is censoring at the Day 28 Visit (last study day for the subject). If the subject is not recovered on this day, the time of the last diary entry will be taken as the time of censoring.

Subjects who discontinue the study before resolving influenza symptoms and have an adverse events being reported as influenzacomplication ongoing on the day of discontinuation of the study will be censored at day 28, 20:00.

For this endpoint the difference of active dosing regimen versus placebo will be estimated using the accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. As baseline covariates the baseline composite score and age category (>=18 - <65 years, >= 65 - <= 85 years) will be included. From this model the ratio of adjusted geometric means and the 95% confidence interval will be derived comparing the active treatment versus placebo.

The Kaplan-Meier estimates will be tabulated and a figure with the Kaplan-Meier curves of the time to resolution of influenza symptoms will be added by treatment group, overall and by age group.

One stratified Cox proportional hazard model will be used to derive the Hazard Ratio for the active treatment in comparison to placebo. A Log (-Log) plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and the Gehan-Wilcoxon method.

All analyses of Time to Resolution of Influenza will also be repeated using all 10 influenza symptoms included in Module 1 of the Flu-iiQ^{TM} instrument.

Kaplan-Meier curves will also be provided for each individual influenza symptom separately.

- **Time to Definitive Resolution of Influenza**
  Time to definitive resolution is defined as the first of a successive series of 2 recordings in which all symptom scores for each of the 2 assessments are 0 or 1 for all 7 primary influenza symptoms of the Flu-iiQ^{TM} (cough, sore throat, headache, nasal congestion, feeling feverish, body aches or pains, and fatigue (tiredness)) AND after which all following assessments also indicate resolution (all symptom scores 0 or 1 for all 7 primary influenza symptoms) or are missing.

Definitions for a successive series of 2 recordings over time are the same as for the Time to Resolution of Influenza. Also censoring will be done similarly as for the Time to Resolution of Influenza.

The Time to Definitive Resolution of Influenza will be analyzed similarly as the Time to Resolution of Influenza.

- **Composite symptom score AUC*:***
  The composite symptom score AUC will be calculated using the daily average symptom scores, from baseline to Day 8 and 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 daily average symptom scores over time of each subject. This approach ensures an optimal approach towards missing data.

  Baseline and post-baseline daily average symptom scores over time will be analyzed using a restricted maximum likelihood based repeated measures approach and using a constrained longitudinal data analysis. The analysis model will include the fixed, categorical effects visit, treatment-by-visit interaction, age category-by-visit interaction and treatment-by-visit-by age category interaction.

  The following list of covariance structures will be applied in the model fit, in the specified order, and the first correlation structure to yield convergence will be applied in the analysis:

  - Unstructured [UN]
  - Ante-dependence [ANTE(1)]
  - Heterogenous Toeplitz [TOEPH]
  - Heterogeneous CS [CSH]
  - Heterogeneous AR(1) [ARH(1)]
  - Toeplitz [TOEP]

  The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

  The composite symptom score AUCs until Day 8 will be based on the Full Analysis set. The model estimates from the model above will be used to estimate the composite symptom score AUCs for each treatment and to derive the difference in the composite symptom score AUCs for active versus placebo overall and by age category.

  A mean ±95% CI plot will also be provided for the estimated average symptom scores over time.

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

The impact of influenza (Flu-iiQ™ Modules 2, 3, 4) will be assessed 2 times a day, from study entry (Baseline, Day 1) through Day 14, and once daily from Days 15 through Day 28 (Safety Follow-up Visit).

- **Composite impact score**
  Per datetime and per module (modules 2, 3 and 4) of the FLU-iiQ™ questionnaire a composite impact score will be calculated as the mean of the non-missing items in each module respectively on a 0-3 scale. Additionally a "total composite impact score" will be calculated as the mean of all non-missing items over all 3 impact score modules together (15 questions). For each time point and composite impact score (module 2, 3,4 and total) a change from baseline will be calculated.If more than 50% of the items to construct a Composite Impact Score are missing, then the value for that composite score for that individual and time point is coded as missing (i.e. 4 or more items missing for module 2, 3 or more items missing for module 3, 3 or more items missing for module 4 and 8 or more items missing for the total composite impact score).

  The composite impact scores will be shown descriptively and by mean (SE) plots per analysis time point.

- **Daily average impact score**
  For the impact modules of the FLU-iiQ™ questionnaire a daily average of the composite impact scores (for modules 2,3,4 and total) and a total average score over the daily averages of the composite impact scores (for modules 2,3,4 and total) will be calculated similar to the daily average symptom scores above.

  The daily averages of the composite impact scores will be shown descriptively and by mean (SE) plots. The total average composite impact scores will be shown only descriptively.

- **Time to resumption of normal activities (usual activities, emotional impact and impact on others)**
  Per module of the FLU-iiQ™ questionnaire on the impact of influenza a time to resumption of normal activities is defined as the time in hours from the first dose of investigational product till the first one of a successive series of 2 recordings where all scores in the FLU-iiQ Module are reported as "no difficulty" (Module 2: usual activities), "not at all" (Module 3: emotional impact) or "not at all concerned" (Module 4: impact on others). If the first record of a successive series of 2 recordings of resumption of normal activities is before day 14 in the evening then the 2 successive recording should have been done over 3 scheduled successive analysis timepoints, 1 missing timepoint is allowed. If the first record of a successive series of 2 recordings of resumption of normal activities is at or after the evening record of Day 14 then the 2 successive recording should have been done within 2 scheduled successive analysis time points.

  Censoring will be done similar to the time to resolution of influenza, taking into account the possible time points a diary entry could have been made after the last observation of difficulties in usual activities, which is 20:00 on the same day if the last observation was a morning diary entry and 8:00 the next day if the last entry was an evening diary entry (Day 1 until Day 14, morning). If the last observation of difficulties in usual activities is on Day 14 in the evening or after Day 14 then the time of censoring is the time of the last diary entry + 24 hours. One exception: if no resumption of usual activities is

observed at Day 28, the time of the last diary entry will be taken as the time of censoring

Data will be presented using Kaplan-Meier curves and Kaplan-Meier estimates by treatment group, overall and by age group. For a comparison between treatment arms, the time to parameters will be analyzed using an accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. As baseline covariates the respective baseline composite impact scores and age category (>=18 - <65 years, >= 65 - <= 85 years) will be included. If the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

4.2.5. FLU-iiQ™ Additional Daily Diary Items

For the 5 additional daily diary items of FLU-iiQ™ frequency distributions of the number (%) of subjects per additional FLU-iiQ™ item and per response category will be shown at baseline and all post-baseline assessments, per treatment group.

4.2.6. Influenza Patient Reported Outcome Diary (FLU-PRO)

- **FLU-PRO total score and FLU-PRO domain scores**

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

  Six FLU-PRO domain scores are computed, representing symptom severity in each of the following body areas: Nose, Throat, Eyes, Chest/Respiratory, Gastrointestinal and Body/Systemic. Each domain score is calculated as the mean of all items comprising the domain, see also Table 8. Each FLU-PRO domain score ranges from 0 to 4.

  These scores will be calculated at each time point a questionnaire was filled. A change from baseline will also be calculated.

  The FLU-PRO scores and changes from baseline will be presented descriptively over time.

Table 8: FLU-PRO domain scores

Domain	Items	Scoring and Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items Daily score for 3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items Daily score for 2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items Daily score for 2 of 3 items must be present to calculate domain score

Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items Daily score for 5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache Vomit (frequency) Diarrhea (frequency)	Arithmetic mean of 4 items Daily score for 3 of 4 items must be present to calculate domain score
Body/Systemic	Headache Head congestion Felt dizzy Lack of appetite Sleeping more than usual Body aches or pains Weak or tired Chills or shivering Felt cold Felt hot Sweating	Arithmetic mean of 11 items Daily score for 8 of 11 items must be present to calculate domain score
Total	All above 32 items	Arithmetic mean of all 32 items within FLU-PRO In the presence of missing data, the above conditions for the calculation of all domain scores must be met in order to calculate the FLU-PRO total score.

Note: The FLU-PRO questionnaire handled according to the protocol is FLU-PRO version 1.0. The calculation of the Total score is done according to the FLU-PRO user manual version 1.1. Hence following questions from the FLU-PRO v1.0 questionnaire will not be used in the analysis: Swollen throat, Difficulty staying asleep, Difficulty falling asleep, Felt lightheaded, Felt uncomfortable (general discomfort).

- **FLU-PRO total score AUC**

  The FLU-PRO total score AUC will be calculated using the FLU-PRO total scores, from baseline to Day 8 and will be estimated for each treatment arm using a mixed model for repeated measurements using a constrained longitudinal data analysis model, similarly as for the composite symptom score AUC in section 4.2.3.

- **Time to return to usual activity and time to return to usual health**

  The time to return to usual activity and the time to return to usual health are defined as the time in hours from the first dose of investigational product till the first one of 2 successive cases where the response is 'Yes' on respectively FLU-PRO additional question 7 and FLU-PRO additional question 9. Missing data within the series are allowed as long as within three successive planned recordings there is at most 1 recording missing.

  In cases where there are no sufficient recordings of return to usual activity/health as defined above, the endpoint will be censored. Censoring will be at the first time of return to usual activity/health, if and only if after this observation there is no recording of difficulties in usual activities/health (ignoring missing recordings). If there are no recordings of return to usual

activity/health satisfying this criterion, the time of censoring is the time of the last diary entry + 24 hours. One exception is censoring at the Day 28 Visit (last study day for the subject). If the subject is not returned to usual activity/health on this day, the time of the last diary entry will be taken as the time of censoring.

Data will be presented using Kaplan-Meier curves and Kaplan-Meier estimates by treatment group, overall and by age group. For a comparison between treatment arms, the time to parameters will be analyzed using an accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. As baseline covariates the ordinal scale at baseline category (ICU, ward+O_2, ward-O_2) and the age category (>=18 - <65 years, >= 65 - <= 85 years) will be included. If the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

- **Time to significant reduction in influenza symptom severity.**
  The time to significant reduction in influenza symptom severity (to mild or none for all influenza symptoms) is defined as time in hours from the first dose of investigational product until the first of 2 successive recordings in which the total score for each of the 2 recordings are lower or equal to 1 and all the domain scores are lower or equal to 1. The 2 successive recordings should have been done within 3 scheduled successive analysis timepoints (one missing in between is allowed).

  Censoring will be done similar to the FLU-PRO time to return to usual activity and time to return to usual health as specified above.
  .

  Data will be presented using Kaplan-Meier curves and Kaplan-Meier estimates. For a comparison between treatment arms, the time to significant reduction in influenza symptom severity will be analyzed using an accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. As baseline covariate the age category (>=18 - <65 years, >= 65 - <= 85 years) and baseline FLU-PRO total score will be included. If the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and Gehan-Wilcoxon method.

- **Proportion of patients with a significant reduction in influenza symptom severity.**
  The proportion of subjects with a significant reduction in symptom severity (the total score for each of the 2 recordings are lower or equal to 1 and all the domain scores are lower or equal to 1) at each assessment will be tabulated.

4.2.7. FLU-iiQ™ Additional Daily Diary Items

For the 9 additional daily diary items of FLU-PRO frequency distributions of the number (%) of subjects per additional FLU-PRO item and per response category will be shown at baseline and all post-baseline assessments, per treatment group.

4.2.8. Correlation between viral load, viral titer and changes in clinical symptoms

- **Correlation between the decline in viral load, the decline in viral titer and clinical symptoms**
  The time to influenza A viral negativity (see definition in section 4.2.2) measured by viral load and viral titer will be correlated with the following clinical measures (see definitions in sections 4.2.3 and 4.2.6):

  1. Time to resolution of symptoms (7 primary symptoms)
  2. Time to resolution of symptoms (All symptoms)
  3. Time to return to usual activity,
  4. Time to return to usual health and
  5. Time to significant reduction in influenza symptom severity

  Scatter plots with smoother curve will be shown per treatment group for the above mentioned correlations. An additional table will be provided showing the spearman correlation coefficients.

- **Correlation between the viral load, viral titer and severity of clinical symptoms**
  The post-baseline log10 values of viral load and post-baseline log10 values of viral titer from day 2 to day 7 will be correlated with the following severity of clinical symptoms (see definitions in sections 4.2.3 and 4.2.6):

  1. Flu-iiQ™ daily average symptom score post-baseline from day 2 to day 7
  2. FLU-PRO total score post-baseline from day 2 to day 7

  Scatter plots with smoother curve will be shown per treatment group for the above mentioned correlations. An additional table will be provided showing the spearman correlation coefficients.

- **Correlation between baseline viral load, baseline viral titer and clinical symptoms**
  The baseline viral load and baseline viral titer will be correlated with the following clinical measures (see definitions in sections 4.2.3 and 4.2.6):

  1. Time to resolution of symptoms (7 primary symptoms)
  2. Time to resolution of symptoms (All symptoms)
  3. Time to return to usual activity,
  4. Time to return to usual health and
  5. Time to significant reduction in influenza symptom severity

Scatter plots with smoother curve will be shown per treatment group for the above mentioned correlations. An additional table will be provided showing the spearman correlation coefficients.

4.2.9. Other Outcomes

- **Time to hospital discharge**

The time to hospital discharge will be calculated from the date of first study drug intake during hospitalization up to the date of discharge. Subjects still hospitalized at the end of the study (end date of hospitalization missing or after trial termination) will be censored at the trial termination date.

Data will be presented using Kaplan-Meier curves and Kaplan-Meier estimates. For a comparison between treatment arms, the time to hospital discharge in days will be analyzed using an accelerated failure time model. The model will use the parametric shape, selected based on the goodness of fit criterion (AIC), and may take a Weibull, log-logistic, lognormal, or gamma distribution. As baseline covariate the age category (>=18 - <65 years, >= 65 - <= 85 years) will be included. If the data don't provide an acceptable model fit, alternatively a Cox proportional hazards model can be used (in case the hazards are proportional). In case a Cox proportional hazards model is used a Log-log plot of survival will be added to check the proportional hazard assumption. Additionally, the time to event data will be analyzed using the logrank test and the Gehan-Wilcoxon method.

4.3. Safety

All safety analyses will be done on the Safety Set. Analyses will be presented overall and by age category and by treatment group.

4.3.1. Adverse events

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing. Treatment-emergent AEs (TEAE) are defined as AEs that were reported or worsened on or after the start of study drug dosing through the 28-day Safety Follow-up Visit.

Adverse events with a start date and time recorded will be allocated based on their start date and time. If there is no time recorded for the start of the adverse event the adverse event that occurred on or after the day of first treatment intake and not after the 28-day safety follow up visit will be considered as treatment-emergent. Only adverse events that occur before the day of first medication intake and after/on the day of signing ICF will be considered as pre-treatment.

In case the start date of an adverse event is partially or completely missing, a worst case allocation will be done using the available date and time information in the start and end date time of the adverse event (i.e. if possible based on the available information the adverse event will be allocated to the treatment phase and hospitalization sub period).

- **Adverse events**

The variables related with adverse events are

- AE term (verbatim and MedDRA preferred term and system organ class)
- Onset date, End date and duration of AE
- Serious AE (Yes/No)
- Severity (Mild, Moderate, Severe, Life threatening)
- Action taken towards study treatment (Dose increased, Dose not changed, Dose reduced, Dose interrupted, Drug withdrawn)
- Relation to study treatment (Not related, Doubtful, Possible, Probable, Very likely)
- Outcome of AE
- AE leading to death (Yes/No)
- Concomitant treatment taken (Yes/No)
- Influenza-related complication (Yes/No)
- Anticipated AE (Yes/No)
- Required hospitalization/prolonged hospitalization (Yes/No)

The adverse events will be shown by MedDRA system organ class and preferred term, in order of descending overall frequency.

Summaries of TEAEs will be presented overall and by the severity of the AE and relationship to the study drug.

AEs leading to death, SAEs, AEs leading to dose interruption, and AEs leading to permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pre-treatment AEs. Spontaneous adverse events reported after the Safety Follow-up Visit, including unresolved, ongoing adverse events will be listed as well.

- **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 (see Appendix 1 for the classification of AEs into Anticipated Events and Anticipated Event Groups):

- 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)

Frequency tabulations of anticipated events and anticipated event groups will be shown by treatment. The Incidence of Treatment Emergent anticipated events will

be compared between active treatment versus placebo by a one-sided Fisher exact test (significance level < 0.10).

- **Influenza-related complications**

Adverse Events reported as influenza-related complications will be tabulated overall and by category and adverse event. A listing showing the AEs reported as influenza-related complications and complication information will be made linking the information to the AE listing.

The categories of influenza related complications as recorded on the eCRF are:

- Bacterial Pneumonia
- Bacterial Superinfections,
- Respiratory Failure,
- Pulmonary Disease
- Cardiovascular and Cerebrovascular Disease.
- Other

4.3.2. Clinical laboratory tests

Laboratory parameters of hematology, serum chemistry and urinalysis will be investigated: All analyses will be done on SI-converted values as available in the database.

In case a laboratory test result is *censored* (no numeric value is available, but only a verbatim term), the following rules are applied:

- '<x' or '>x': a numeric value will be imputed by a value exceeding the cut-off value with one unit
- '≤x' or '≤x': imputation by x.

The laboratory abnormalities will be determined according to the criteria specified in the WHO grading table (see Appendix 2), available toxicity grades in the laboratory raw data will not be used. In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades/abnormalities the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period for each trial phase separately, including all post-reference scheduled and unscheduled measurements of that phase.
- The abnormalities "abnormally low" and "abnormally high" are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high value post-reference, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)
- If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations.

Actual values and change from baseline will be summarized by treatment group at each scheduled time point.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent in a particular phase if it is worse than the reference corresponding to this phase. If the reference is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at reference to "abnormally high" post reference (or vice versa) is also treatment-emergent. The treatment emergent definition is applicable in both, the treatment and follow-up phase.

The number and percentage of subjects will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, a cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and follow-up phase. This table will also show the number and percentage of subjects per worst toxicity/abnormality, the number and percentage of subjects per treatment-emergent worst toxicity/abnormality, and the cumulative number of subjects per treatment-emergent toxicity/abnormality or worse.

Mean ± SE graphs over time for the actual values and changes from reference will be generated for all tests performed.

A listing of abnormal individual subject hematology and clinical chemistry values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding subject/parameter.

Grade 2 or higher toxicity laboratory values will be listed separately.

Urinalysis results will be listed. Proteinuria and urine WBCs will be summarized.

4.3.3. Electrocardiograms

PR duration, QT duration,, QRS duration, Heart Rate and QTc intervals using Bazett's correction formula and Fridericia's correction formula will be investigated. QTc values will be used as reported, they will not be recalculated.

The actual values of QT/QTc will be categorized into abnormalities using the boundaries defined in the table below:

Abnormality codes:	*QT/QTcorrected*
"Normal"	≤450 ms
"]450 ms, 480 ms]"	450 ms< QTc ≤ 480 ms
"]480 ms, 500 ms]"	480 ms< QTc ≤ 500 ms
"More than 500 ms"	QTc > 500 ms

Abnormalities on the change from reference will be defined for QT/QTc, as follows

- < 30 ms (Normal)
- [30; 60] ms
- > 60 ms.

Only increases by ≥ 30 ms will be considered as abnormalities. (Note: the QTc definitions for abnormalities follow the ICH E14 guidance.)

Worst abnormalities are determined over the whole observational period for each trial phase separately, including all post-reference scheduled and unscheduled measurements of that phase.

An abnormality will be considered treatment-emergent in a particular phase if it is worse than the reference corresponding to this phase. If the reference is missing, the abnormality is always considered as treatment-emergent. Abnormalities on changes from reference are always defined as treatment-emergent.

Actual values and change from baseline will be summarized by treatment group at each scheduled time point.

The number and percentage of subjects will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, a cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and follow-up phase. This table will also show the number and percentage of subjects per worst toxicity/abnormality, the number and percentage of subjects per treatment-emergent worst toxicity/abnormality, and the cumulative number of subjects per treatment-emergent toxicity/abnormality or worse.

Mean ± SE graphs over time for the actual values and changes from reference will be generated for all tests performed.

A tabulation of the worst QT/QTc change versus baseline per treatment per phase will be presented.

Abnormal individual subject ECG values or abnormalities on the changes will be listed.

4.3.4. Vital Signs

Systolic and Diastolic blood pressure, oral temperature, pulse rate, respiratory rate, arterial oxygen saturation and level of consciousness will be investigated.

Vital Signs abnormalities will be determined according to the WHO grading scale and the boundaries defined in Appendix 3.

Worst toxicities are determined over the whole observational period for each trial phase separately, including all post-reference scheduled and unscheduled measurements of that phase.

Actual values and change from baseline will be summarized by treatment group at each scheduled time point. A toxicity will be considered treatment-emergent in a particular phase if it is worse than the reference corresponding to this phase. If the reference is missing, the abnormality is always considered as treatment-emergent.

The number and percentage of subjects will be shown in a cross-tabulation of the toxicity/abnormality post-baseline versus baseline at each scheduled time point.

Additionally, a cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and follow-up phase. This table will also show the number and percentage of subjects per worst toxicity/abnormality, the number and percentage of subjects per treatment-emergent worst toxicity/abnormality, and the

cumulative number of subjects per treatment-emergent toxicity/abnormality or worse.

Mean ± SE graphs over time for the actual values and changes from reference will be generated for all tests performed.

A listing of abnormal individual subject VS values will be provided.

4.3.5. *NEW Score*

The NEW Score is an aggregated score with a range from 0 to 20 calculated as the sum of the scores per parameter (see Table 9). In case information for a parameter is missing the NEW score cannot be calculated. Descriptive statistics of the NEW score and the change from baseline will be shown by analysis time point. Additionally a mean +/- SE graph of the scores over time will be provided.

The NEW score will be categorized into its clinical risk according to the following categories:

- Low clinical risk: (score 1 – 4)
- Medium clinical risk: (score 5 – 6, or 1 individual parameter with a score 3)
- High clinical risk: (score 7 and more)

A tabulation of the clinical risk categories will be made per analysis time point.

Table 9: National Early Warning Score (NEWS)*

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level Of Consciousness				A			V,P, or U

*The NEWS initiative flowed from the Royal College of Physicians' NEWS Development and Implementation Group (NEWSDIG) report, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation

4.3.6. *Physical Examinations:*

Abnormal physical examination results will be listed only.

4.4. Virology

4.4.1. Viral Phenotype

The JNJ-63623872 EC_{50} and Oseltamivir IC_{50} with their fold change values will be analyzed at baseline and at the subject's last study visit (FC = fold change in EC50 (IC50) value).

- The last study visit is defined as the last time point for which an EC50 and/or IC50 result is available.
- FC is calculated as the EC_{50} (or IC_{50}) divided by the reference. If the patient EC_{50} (or IC_{50}) is censored, the fold change value get the same censor, e.g. patient EC_{50} = >20 nM, reference EC_{50} = 4nM, Fold Change value >5.

The following output will be provided overall and by influenza subtype category:

- Emerging phenotypic resistance: descriptive statistics for FC in EC_{50} and IC_{50} value for JNJ-63623872 and oseltamivir respectively at baseline and the last study visit. The number (%) of subjects by treatment arm with censored phenotype data at baseline and the last study visit will also be shown.
- Descriptive statistics for fold change ratio of last study visit versus baseline including geometric mean and 95% CI.
- A listing showing viral load data together with phenotype data (EC_{50}, IC_{50} and fold change values) per subject and influenza subtype for all available time points including screening/baseline.

4.4.2. Viral Genotype

Assessment of viral sequences will be done to determine amino-acid sequence changes that may be associated with resistance to JNJ-63623872 and/or oseltamivir. To that end, genotypic data for PB2, NA and optionally other genome segments of the influenza virus will be gathered.

All positions in the gathered regions will be analyzed.

The following 12 amino-acid positions in PB2 are of interest: Q306, F323, S324, F325, S337, H357, F363, K376, F404, Q406, M431, and N510.

The following resistance associated mutations in NA are of interest:

- For subtype H1N1: D199N, I223R, H275Y, and N295S
- For subtype H3N2: E119V, H274Y, R292K, and N294S

The list of positions of interest might be updated during the analysis.

A mutation is treatment-emerging at a specific (post-baseline) time-point if the amino-acid of the considered position is absent at screening/baseline and present at that time point.

The baseline is the collection of all polymorphisms present at any time point up to the first intake of study.

Data will be summarized using frequency tabulations (n and %). Displays and individual mutations should be presented overall and by influenza subtype category and for PB2 and NA separately. The following output will be provided:

- Baseline polymorphisms: number (%) of subjects with available genotype data, with any baseline polymorphism, and the number of subjects per polymorphism, for all polymorphisms, per treatment arm.
- Baseline polymorphisms: number (%) of subjects with any baseline polymorphism and with specific baseline polymorphisms at the positions of interest.
- Frequency tabulations for the presence of all emerging mutations overall post baseline.
- Frequency tabulations for the presence of all emerging mutations overall post baseline at positions of interest.
- Listing for genotype data per subject for all available time points including screening/baseline including viral load data (include influenza subtype and influenza subtype category).

4.5. Health Care

The number of subjects admitted to the Intensive Care Unit (ICU) after baseline will be tabulated.

The length of ICU stay for subjects transferred to the ICU after baseline is calculated as:

End date in ICU – Start date in ICU +1.

If a subject has multiple periods in the ICU the durations for these separate stays in the ICU will be summed.

Descriptive statistics of the duration in the ICU will be shown for all subjects that were admitted to the ICU after baseline.

References

Bacci E.D., Kim K., Stringer S., Leidy N.K. (18 Dec 2015 v1.1) User Manual for the InFLUenza Patient-Reported Outcome (FLU-PRO) Diary, Leidos Biomedical Research in support of the National Institute of Health, National Institute of Allergy and Infectious diseases, Division of Clinical Research

Royal College of Physicians of London. (2012) National early warning score (NEWS): standardising the assessment of acute-illness severity in the NHS.. www.rcplondon.ac.uk/resources/national-earlywarning-score-news

Guideline, I. H. T. (2006). The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. Recommended for adoption at Step, 4

White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: issues and guidance for practice. Statistics in medicine, 30(4), 377-399.

World Health Organization. (2003) "WHO toxicity grading scale for determining the severity of adverse events."

Appendix 1 Anticipated Events and Anticipated Event Groups

Table 10 shows an overview of the anticipated event groups with group number.

Table 11 indicates which adverse event preferred terms (MedDRA PT) are Anticipated Events (AnE) and Closely Related Medical Events (ME). These adverse events will be classified as an Anticipated Event according to the protocol term and are grouped into Anticipated Event Groups. One adverse event can be added to one or two groups according to Table 11.

Table 10: Anticipated Event groups

Group Number	*Grouped Term*
Group 1	Infections and infestations
Group 2	Bacterial Pneumonia
Group 3	Bronchitis
Group 4	Sinus infection
Group 5	Ear infection
Group 6	Worsening of asthma, asthma attack
Group 7	COPD exacerbation
Group 8	Complications of sickle cell disease, sickle cell crisis
Group 9	Diabetic complications
Group 10	Acute Respiratory Distress Syndrome (ARDS)

Table 11: Anticipated Events (AnE) and Closely Related Medical Events (ME).

Protocol Term Anticipated Event	*AnE*	*ME*	*MedDRA PT*	*MedDRA Code**	*Anticipated Event Grouped Term*	*Group Number*
Bacterial pneumonia	☒	☐	Pneumonia bacterial	10060946	Infections and infestations/Bacterial Pneumonia	1/2
Bacterial pneumonia	☐	☒	Enterobacter pneumonia	10054218	Infections and infestations/Bacterial Pneumonia	1/2
Bacterial pneumonia	☐	☒	Pneumonia haemophilus	10035702	Infections and infestations/Bacterial Pneumonia	1/2
Bacterial pneumonia	☐	☒	Pneumonia staphylococcal	10035734	Infections and infestations/Bacterial Pneumonia	1/2

Bacterial pneumonia	☐	☒	Pneumonia streptococcal	10035735	Infections and infestations/Bacterial Pneumonia	1/2
Bronchitis	☒	☐	Bronchitis	10006451	Infections and infestations/Bronchitis	1/3
Bronchitis	☐	☒	Bronchitis bacterial	10061736	Infections and infestations/Bronchitis	1/3
Bronchitis	☐	☒	Bronchitis haemophilus	10006460	Infections and infestations/Bronchitis	1/3
Sinus infection	☒	☐	sinusitis[a]	10040753	Infections and infestations/Sinus infection	1/4
Sinus infection	☐	☒	Acute sinusitis[1]	10001076	Infections and infestations/Sinus infection	1/4
Sinus infection	☐	☒	Chronic sinusitis	10009137	Infections and infestations/Sinus infection	1/4
Sinus infection	☐	☒	Viral sinusitis	10051513	Infections and infestations/Sinus infection	1/4
Ear infection	☒	☐	Ear infection	10014011	Infections and infestations/ Ear infection	1/5
Ear infection	☐	☒	Middle ear effusion	10062545	Infections and infestations/ Ear infection	1/5
Ear infection	☐	☒	Otitis externa	10033072	Infections and infestations/ Ear infection	1/5
Ear infection	☐	☒	Otitis media	10033078	Infections and infestations/ Ear infection	1/5
Ear infection	☐	☒	Otitis media acute	10033079	Infections and infestations/ Ear infection	1/5
Worsening of asthma, asthma attack[b]	☒	☐	Asthma	10003553	Worsening of asthma, asthma attack	6
Worsening of asthma, asthma attack[2]	☐	☒	Asthmatic crisis	10064823	Worsening of asthma, asthma attack	6
COPD exacerbation [c]	☐	☒	Chronic obstructive pulmonary disease	10009033	COPD exacerbation	7
COPD exacerbation [3]	☐	☒	Emphysema	10014561	COPD exacerbation	7
Complications of sickle cell disease, sickle cell crisis[d]	☐	☒	Sickle cell anaemia	10040641	Complications of sickle cell disease, sickle cell crisis	8
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Acute chest syndrome	10051895	Complications of sickle cell disease, sickle cell crisis	8

[a] Infectious etiology only

[b] Please note that asthma aggravated codes to a PT of asthma. These PTs will be considered as anticipated events only if the subjects have documented those conditions (such as: asthma, COPD, Sickle cell disease, or diabetes) before enrolling the study.

[c] Please note that chronic obstructive airways disease exacerbated codes to a PT of chronic obstructive pulmonary disease. These PTs will be considered as anticipated events only if the subjects have documented those conditions (such as: asthma, COPD, Sickle cell disease, or diabetes) before enrolling the study.

[d] These PTs will be considered as anticipated events only if the subjects have documented those conditions (such as: asthma, COPD, Sickle cell disease, or diabetes) before enrolling the study.

Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Pain	10033371	Complications of sickle cell disease, sickle cell crisis	8
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Ischaemic stroke	10061256	Complications of sickle cell disease, sickle cell crisis	8
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Embolic stroke	10014498	Complications of sickle cell disease, sickle cell crisis	8
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Deep vein thrombosis	10051055	Complications of sickle cell disease, sickle cell crisis	8
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Pulmonary embolism	10037377	Complications of sickle cell disease, sickle cell crisis	8
Complications of diabetes mellitus, diabetic ketoacidosis[e]	☒	☐	Diabetic complications	10061104	Diabetic complications	9
Complications of diabetes mellitus, diabetic ketoacidosis[5]	☐	☒	Diabetic ketoacidosis	10012671	Diabetic complications	9
Complications of diabetes mellitus, diabetic ketoacidosis[5]	☐	☒	Diabetes mellitus[f]	10012601	Diabetic complications	9
Complications of diabetes mellitus, diabetic ketoacidosis[5]	☐	☒	Diabetic ketoacidotic hyperglycaemic coma	10012672	Diabetic complications	9
Complications of diabetes mellitus, diabetic ketoacidosis[5]	☐	☒	Hypoglycaemia	10020993	Diabetic complications	9
Acute Respiratory Distress Syndrome (ARDS)	☒	☐	Acute respiratory distress syndrome	10001052	Acute Respiartory Distress Syndrome (ARDS)	10
Acute Respiratory Distress Syndrome (ARDS)	☐	☒	Acute respiratory failure[g]	10001053	Acute Respiartory Distress Syndrome (ARDS)	10

[e] These PTs will be considered as anticipated events only if the subjects have documented those conditions (such as: asthma, COPD, Sickle cell disease, or diabetes) before enrolling the study.
[f] Please note that diabetes mellitus aggravated and diabetes mellitus exacerbated codes to a PT of diabetes mellitus
[g] This event will be considered anticipated only if it occurs in the context of ARDS

Appendix 2 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

Item	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Item	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Item	Grade 1	Grade 2	Grade 3	Grade 4
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
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	>40.5 °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

Appendix 3 WHO grading scale Vital Signs

The following abnormalities are defined for vital signs:

	Vital Signs parameter		
Abnormality Code	**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	-	-

* The classification of AEs related to hypotension and hypertension will be done according to the WHO grading scale