Janssen Research & Development *

Statistical Analysis Plan
Amendment 1

A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pimodivir in Combination With the Standard-of-care Treatment in Adolescent, Adult, and Elderly Hospitalized Patients With Influenza A Infection

Protocol 63623872FLZ3001; Phase 3

JNJ-63623872-ZCD (Pimodivir)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Amendment 1 (1 July 2020)

The overall reason for the amendment: The overall reason for the amendment is to make general updates to the text including minor grammatical, formatting, or spelling changes throughout the SAP for clarification purposes and to align with protocol amendment 2. A new section is added: to include analysis of pharmacokinetic parameters and pharmacodynamic analyses. Three new subgroups were added namely influenza season, study period (before interim, after interim) and COVID-19 impacted (Yes/No). To assess the impact of COVID-19, several tables and listings are added presenting the COVID-19 impacted subjects separately. Two new secondary endpoints based on a clinically relevant change from baseline in EQ-5D VAS are included. A new endpoint related to the HRS is added: the fundamental hospital recovery scale, reflecting the actual location/situation, which will be analysed each day from Day 2 to 14. Additionally, the following four new secondary endpoints were also added: time to NEWS2 ≤ 2, time to clinical improvement, time to clinical failure and incidence of mortality per day.

The table below gives an overview of the changes in all applicable sections

Summary of changes: An additional analysis set was defined for the analysis of the primary endpoint and the six most important secondary endpoints. Additional analysis sets were defined for the pharmacodynamic analyses and the analysis of pharmacokinetics parameters. The criterion: "Subjects did not switch to another influenza antiviral as a part of the SOC during the treatment period" was added and the criterion: "subjects that did not use a concomitant medication that may have affected the efficacy of the study drug" was removed from the definition of the per protocol analysis set. The in- and exclusion criteria needed to define the per protocol analysis set are updated and added.

2.2.2 Efficacy Analysis Sets
2.2.2.2 Per Protocol Set (PP)
2.2.2.3 Intent-To-Treat non-infected (ITT-ni) Set
2.2.4 Pharmacokinetics Analysis Set
2.2.5 Pharmacodynamics Analysis Set

Summary of changes: Baseline resistance categories were defined based on influenza polymerase basic protein 2 genotype and phenotype. General re-formatting to assist readability of the section. The subgroups influenza season, study period (pre- and post-interim) and COVID-19 impacted (yes/no) are added.

2.3 Definition of Subgroups

Summary of changes: Detailing the definition of baseline ECG measurement was added. The baseline HRS is clarified. The last study visits for vital signs, NEWS2, ECG and central laboratory parameters are also defined.

2.5 Baseline and Endpoint

Summary of changes: A new section (2.6) was added to describe details of the analysis to support marketing authorization approval by FDA and EMA where a subset of patients is used with oseltamivir use as part of their SOC treatment and to include text to allow for potential analyses for other regions or countries

2.6 Other Definitions

Summary of changes: The number of subjects impacted by COVID-19 are added in the disposition table per analysis set. The table showing the number of subjects that discontinued is extended to show the number of subjects that discontinued due to COVID-19. Missed visits or changed visits due to COVID will also be presented. A listing showing the exposure to study drug for subjects impacted by COVID-19 is added. Major and minor protocol deviations related to COVID-19 are included. Concomitant therapy that was taken for COVID-19 infection are presented in an additional table.

4 SUBJECT INFORMATION

4.1 Demographics and Baseline Characteristics

4.2 Disposition Information

4.4 Extent of Exposure

4.5 Protocol Deviations

4.6 Prior and Concomitant Medications

Summary of changes: A new section (5.1.3) was added to describe how the actual values of the stratification factors are derived.

5.1.3 Stratification Factors

Summary of changes: The text describing the estimand is updated to align with the ICH E9 addendum guidance and to include MI methods for missing HRS values due to COVID-19 and not due to COVID-19

5.2.2 Estimand

Summary of changes: the multiple imputation methods are applied on the missing HRS values at day 6 due to COVID-19 and to missing HRS values on day 6 not due to COVID-19 in case the prevalence is more then > 5%. A table is added to show the number (%) missing HRS values on day 6 by reason of missing.

5.2.3 Analysis Methods

Summary of changes: The fundamental hospital recovery scale, reflecting the actual location/situation of the subject evaluated daily from Day 2 to Day 14 is added. Time to NEWS2 ≤ 2, time to clinical improvement, time to clinical failure and incidence of mortality per day are

added secondary endpoints. Re-hospitalizations are defined at the description of time to hospital discharge.

5.3.1.1 Clinical Outcome

Summary of changes: Adverse events leading to study discontinuation, AEs, serious AEs and non-serious AEs related to COVID-19 were added to the list for the adverse events summary table. The definition of a treatment emergent AE was detailed. A table of influenza related complications as assessed by the investigator was added. Tables that show AEs related to COVID-19 infection, SAEs related to COVID-19 infection, AEs related to COVID-19 infection leading to death and a listing showing the AEs related to COVID-19 infection are added.

7.1.1 Definitions

7.1.2 Analysis Methods

Summary of changes: The change from baseline in EQ-5D VAS is categorized in two ways providing two additional endpoints.

5.3.1.3 Other Patient Reported Outcome

Summary of changes: A bootstrapping method for calculating **t**he median time to event with 95% confidence interval from the accelerated failure time model was added.

5.3.2 Analysis Methods

Summary of changes: Additional details regarding number of loose stools per day and stool consistency will be collected for subjects who report diarrhea adverse events. A confirmed diarrhea event is defined and the analysis of these events is described.

7.1.1 Definitions

7.1.2 Analysis Methods

Summary of changes: The use and definition of NEWS2 is explained and added.

NEWS2 will be used in the analyses.

7.6 NEW Score

Summary of changes: A new section was added to describe the analysis of the pharmacokinetic parameters and to explore their relationships with efficacy and safety.

9 Pharmacokinetics/Pharmacodynamics

9.1 Pharmacokinetics

9.2 Pharmacokinetic/Pharmacodynamic Relationships

Summary of changes: the anticipated events table has been corrected for a typo and to include an additional MedDRA preferred term for diabetic complications

Attachment 1

ABBREVIATIONS

ACVPU	Alert, new confusion, voice, pain, unresponsive
AE	adverse event
AFT	accelerated failure time
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{12h}	area under the plasma concentration-time curve from time 0 to 12 hours
bid	bis in die; twice daily
BMI	body mass index
CI	confidence interval
C_{max}	maximum plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CTP	clinical trial protocol
C_{trough}	Plasma concentration just prior to the beginning or at the end of a dosing interval
CV	coefficient of variation
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ePRO	Electronic Patient-reported outcome (Device used for recording of patient-reported outcomes)
EQ-5D	European Quality of Life 5 Dimensions
FDA	Food and Drug Administration
GMR	geometric mean ratio
HRS	Hospital recovery scale
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
ITT	Intent-To-Treat
ITT-i	Intent-To-Treat infected
ITT-ni	Intent-To-Treat non-infected
IWRS	Interactive web response system
LOD	limit of detection
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MT	Mid-turbinate
NAI	neuraminidase inhibitor
NEWS	National early warning score
NEWS2	National early warning score 2
OST	oseltamivir
PA	Polymerase acidic protein
PB2 (1)	polymerase basic protein 2 (1)
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PP	Per Protocol
PT	preferred term
qRT-PCR	quantitative real time polymerase chain reaction
SDTM	Subject Data Tabulation Model
SAE	serious adverse event
SAP	statistical analysis plan

SBP	systolic blood pressure
SI	international system
SOC	standard of care
SSG	Statistical support group
TEAE	Treatment Emergent Adverse Events
T_{max}	Time to reach C_{max}
VAS	Visual analogue scale

1. INTRODUCTION

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 pimodivir (JNJ-63623872). Separate documents for mock shells and table of contents for TFLs (DPS) are also produced. The SAP is to be interpreted in conjunction with the protocol.

Pimodivir (formerly known as VX-787 and JNJ-63623872) 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 3 development as treatment for influenza A infection.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate superiority of pimodivir in combination with standard-of-care (SOC) treatment compared to placebo in combination with SOC treatment on Day 6, with respect to the clinical outcome on the hospital recovery scale.

Secondary Objectives

The secondary objectives are:

- To investigate the safety and tolerability of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the time from start of study drug to hospital discharge in subjects treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the time from intensive care unit (ICU) admission to ICU discharge in subjects treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the time from start to end of mechanical ventilation in subjects treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment each separated day from Days 2 to 14 (excluding the primary time point), with respect to the clinical outcome on the hospital recovery scale.
- To evaluate superiority with respect to the time to return to daily activities in subjects treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the incidence of complications associated with influenza after the start of study treatment in subjects treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To investigate all-cause mortality in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.

- To investigate the incidence and duration of antibiotic treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the number (proportion) of subjects needing extended treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the number (proportion) of subjects requiring re-hospitalization in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the number (proportion) of subjects not hospitalized at Day 6 in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to clinical response in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to improvement of respiratory status in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To assess the pharmacokinetics (PK) of pimodivir and to explore the PK/pharmacodynamics (PD) relationships of pimodivir for efficacy and safety.
- To investigate the acceptability (taste and swallowability) of the pimodivir formulation in adolescents.
- To evaluate superiority with respect to the following influenza A viral parameters in the pimodivir treatment arm compared to the control arm by qRT-PCR and viral culture:
  - Time to viral negativity.
  - Viral load over time.
- To investigate the emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.

1.2. Trial Design

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with SOC treatment vs placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to ≤85 years) hospitalized subjects with influenza A infection. A target of 600 hospitalized influenza A-infected subjects will be randomly enrolled in this study with 300 subjects planned per treatment arm. The aim is to enroll a minimum of 60 adolescent subjects in this study in selected countries and study sites consistent with local regulations. The randomization will be stratified for screening NEWS2 (4-5 or >5) (NEWS is changed to NEWS2 per CTP amendment 2), type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of influenza symptoms (first administration of study drug within 72 hours or between 72 and 96 hours since onset of influenza symptoms). The study population should consist of at least 75% of subjects

(75% of the total planned sample size of 600 subjects) with first administration of study drug ≤72 hours since onset of influenza symptoms.

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

- Treatment Arm 1: pimodivir 600 mg bid for 5 days + SOC treatment*
- Treatment Arm 2: pimodivir placebo bid for 5 days + SOC treatment*

*SOC treatment is determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. For further details see protocol Section 3.1.

1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint is the hospital recovery scale as assessed on Day 6. The alternative hypothesis is that the outcome on the hospital recovery scale with pimodivir in combination with SOC treatment is statistically superior to treatment with placebo in combination with SOC treatment on Day 6 in hospitalized subjects with influenza A infection.

1.4. Sample Size Justification

The study will enroll 600 subjects between the ages of 13 and 85 years, inclusive. Subjects will be randomized 1:1 to one of the treatment arms.

The sample size is based on the primary endpoint of the hospital recovery scale at Day 6. Based on the proportional odds model and assuming a benefit of approximately 38% reduction of the common odds ratio, a total sample size of 600 subjects (randomized 1:1) is required to obtain a power of 90% [11]. Inclusion of stratification factors would provide some improvement on the derived power.

In the sample size calculation it is assumed that the distribution of subjects treated with placebo in combination with SOC treatment will be as follows on Day 6:

- Not hospitalized: 30%
- Non-ICU hospitalization, not requiring supplemental oxygen: 30%
- Non-ICU hospitalization, requiring supplemental oxygen: 25%
- Admitted to the ICU, not requiring invasive mechanical ventilation: 5%
- Requiring invasive mechanical ventilation: 5%
- Death: 5%

This sample size is robust to mild to moderate changes in this distribution.

1.5. Randomization and Blinding

Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio 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 for NEWS2 (4-5 or >5) (NEWS

is changed to NEWS2 per CTP amendment 2) at screening, type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of influenza symptoms (first administration of study drug ≤72 hours or between 72 and 96 hours since onset of influenza symptoms). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

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

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

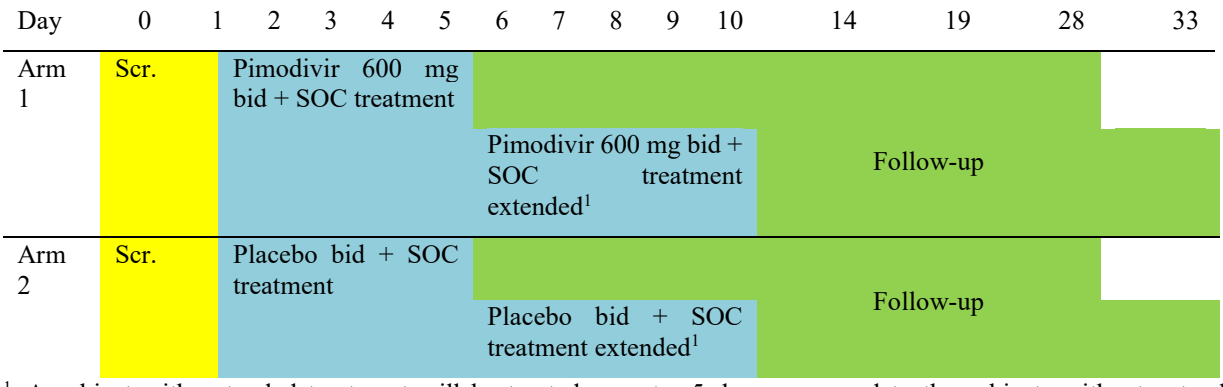
2. GENERAL ANALYSIS DEFINITIONS

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

2.1. Visit Windows, Phase Definitions and Baseline

The study is set up as shown in Figure 1. The phases will be constructed as shown in Table 1.

Figure 1: Study time line.



[1] A subject with extended treatment will be treated an extra 5 days compared to the subjects without extended treatment.

Note: Depending on the time of screening/enrollment, subjects will receive 1 dose (evening) or 2 doses (morning and evening) of study drug on Day 1. For subjects who receive only 1 dose of pimodivir or placebo on Day 1 (evening), dosing should continue until the morning of Day 6 so that all subjects receive 10 doses in total, or for subjects with extended treatment until the morning of Day 11, so all subjects with extended treatment receive 20 doses in total.

2.1.1. Phase Definitions

Table 1: Construction of phases

Trial phase	***Trial subperiod**[*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 drug intake
Treatment (phase 2)		Datetime of first study drug intake [*4]	Datetime of last study drug intake[*4] + 24 hours
	Planned Treatment (subperiod 1)[*2]	Datetime of first study drug intake [*4]	If extended treatment then Datetime of first study drug intake in extended treatment subperiod – 1 minute Else Datetime of last study drug intake[*4] + 24 hours
	Extended Treatment (subperiod 2)[*3]	Datetime of first study drug intake in extended treatment subperiod[*4]	Datetime of last study drug intake[*4] + 24 hours
Follow-up (phase 3)		End of the treatment phase +1 minute	Trial termination date (or date of last contact if later)

[*1]: A treatment period will be constructed in the derived datasets with the same start and end date as the treatment phase.
[*2]: The planned treatment subperiod will be present for all treated subjects.
[*3]: The extended treatment subperiod will only be present for all subjects with extended treatment.
[*4]: In case the time part of the study drug intake is missing the imputed time part will be used as described below.

Additionally, the treatment phase and follow-up phase will be combined in the analysis.

In case the time part of first study drug intake is missing the randomization time will be used. In case the time part of the randomization time is also missing we impute the time part with 8:00 if taken in the morning or with 20:00 if study drug was taken in the evening. In case the time of the last study drug intake is missing, the time part will be imputed with 8:00 if the last study drug was taken in the morning or with 20:00 if the last study drug was taken in the evening.

In case the time part of first intake of the treatment extension is missing, the time part will be imputed with 8:00 if the last study drug of the planned 5 days of treatment was taken in the morning or with 20:00 if the last study drug 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 (or date of last contact if later).

Assessments will be assigned to phases and subperiods based on their start datetime, but seconds will not be taken into account. If only one assessment is expected per day and 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 00:00 of the day of the assessment (except for Adverse Events see details in Section 7.1). No imputations on missing times/time parts will be made in the analysis datasets.

In case more than one assessment per day is expected and time part is missing:

1. Allocate according to the timepoint: Morning=00:00, Middle of the day=12:00, Evening=20:00

2. If 1 timepoint is missing on day x: Check the non-missing timepoints of the other records on this day x. Allocate this record to the timepoint of day x that is not already covered. Then apply 1.

3. If 2 timepoints are missing on day x: Check the non-missing timepoint of the other record on this day x. Allocate these records to the timepoints of day x that are not already covered, assigning the smallest XXSPID value to the earlier timepoint and the larger XXSPID value to the later timepoint. Then apply 1.

4. If 3 timepoints are missing on day x: allocate using the values of XXSPID, i.e. lowest number is morning, next is middle of the day, highest number is evening. Then apply 1.

2.1.2. Analysis Visits

In general, AVISIT will be derived as the day of a scheduled visit, assessment or self-assessment as recorded in the respective SDTM, including the safety follow-up visit and day 28 final study visit (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 specifications on the baseline record and endpoint record see Section 2.5.

For post-baseline assessments of the Daily Activities Resumption (Return to daily activity), Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC) and

the European Quality of Life 5 Dimensions (EQ-5D) questionnaires, AVISIT and AVISITN will be derived from the number of days in the study relative to the start of study treatment (reldy, see Section 2.4). Post-baseline assessments taken from 00:00 until 02:00 will be assigned to the day before (e.g. a recording on Day 4 at 01:00 will be assigned AVISIT= Day 3).

2.1.3. Analysis Timepoints

For parameters that were assessed more than once daily, the analysis timepoint (ATPT) will be the timepoint as reported in the database. In case there are multiple records per planned timepoint take the last in time.

For hospitalized subjects we expect 3 assessments per day. If the timepoint is missing but the date time is known, then we impute as follows:

If date time is within [00:00, 11:00] then allocate the morning timepoint
If date time is within [11:01, 16:00] then allocate the midday timepoint
if date time is within [16:01, 23:59] then allocate the evening timepoint
For subjects that are discharged we expect only 1 vital sign assessment. Therefore in case the timepoint is filled in, we set it to empty.

For NEWS2, select for each of the parameters one record per timepoint as described above. The date and time of the NEWS2 will be derived from the last date time of each of the parameters and this will be used to allocate the NEWS2 to a phase. A subject received oxygen at the planned timepoint if the date time of the oxygen saturation measurement falls within the period that the subject received supplemental oxygen.

2.1.4. Use of Records per Analysis Visit and Timepoint

To ensure only one record is used per analysis visit for the Return to daily activity and PGIS questionnaires only one questionnaire should be selected for analysis. Following rules should be followed to select the questionnaire.

1. The questionnaire latest in time is used.
2. If more than one questionnaire is still selected, the questionnaire with the highest sequence number is used.

To ensure only one record is used per analysis visit for the PGIC and EQ-5D questionnaires the following rules should be followed to select the questionnaire.

Listed below (Table 2) are the visit windows and the target days for each visit where PGIC and EQ-5D are recorded. The reference day is Study Day 1, the date of first intake of study drug.

1. If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window.
2. If 2 actual visits are equidistant from the target day within a visit window, the later visit in time is used.

Table 2: Visit Windows for PGIC and EQ-5D

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
6	Day 6	[2 to 10]	6
14	Day 14	[11 to 20]	14
28	Day 28	[21 to 38]	28
For subjects on extended treatment:			
14	Day 14	[11 to 16]	14
19	Day 19	[17 to 22]	19
33	Day 33	[23 to 38]	33

*Relative to Study Day 1

2.1.5. Unscheduled Assessments

In general, all scheduled assessments after first administration of study drug 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 first dose unscheduled assessments will be taken into account for worst-case determination.

For PRO assessments, both scheduled and unscheduled assessments will be taken into account to determine which assessment will be used per analysis visit / timepoint as described in Section 2.1.4.

For time to response endpoints, recordings taken at unscheduled visits will be taken into account unless indicated differently.

2.2. Analysis Sets

2.2.1. All Randomized Analysis Sets

2.2.1.1. All Randomized Analysis Set (RAND)

All randomized subjects with a randomization date time at or before the date time of first intake of study drug, or with a randomization date time and no study drug intake.

2.2.1.2. Randomized and/or Treated Analysis Set (RT)

All randomized subjects and/or all subjects who received at least 1 dose of study drug. The Randomized and/or Treated Analysis Set (RT) will be used in all listings unless specified otherwise for a specific display.

2.2.2. Efficacy Analysis Sets

Efficacy will be analyzed on the intent-to-treat infected (ITT-i) set and by randomized treatment. The primary efficacy endpoint will also be analyzed on the Per Protocol set. The primary efficacy endpoint and the six most important secondary endpoints (all endpoints included in the hierarchical

testing procedure at the final analysis) will also be analyzed on the intent-to-treat non-infected (ITT-ni) set and by randomized treatment.

2.2.2.1. Intent-To-Treat infected (ITT-i) set

All subjects from the RAND analysis set who receive at least 1 dose of study drug and who have a confirmed infection with influenza A. Confirmation of Influenza A infection will be obtained from virology data. If there are no virology data available at the final analysis, then a subject will be excluded from the ITT-i set. Analysis on the ITT-i set will be analyzed as randomized.

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 at baseline or pre-baseline;

else

- at least two positive PCR results from central lab testing post-baseline;

else

- at least one positive result from local lab testing for influenza A at baseline or pre-baseline, provided that no central lab testing is available at baseline or pre-baseline.

Note: viral load (PCR) results from central lab testing recorded as 'TARGET NOT DETECTED' will be considered as negative, all other non-missing results as positive (i.e. between LOD and LOQ, or quantifiable (above LOQ)).

Note: If no viral load measurement is available prior to first study drug intake then the first viral load result from the central lab testing obtained up to and including 30 minutes after first dose of study drug will be considered as the baseline assessment. If no baseline central lab measurement is available, the first viral load result from the local lab test obtained up to and including 30 minutes after first dose of study drug will be considered as the baseline local test assessment in case no local lab test is available at baseline or pre-baseline.

Note: viral load results from the central lab testing obtained from leftover samples from the local virology test will be considered in determining confirmed infection with influenza A.

2.2.2.2. Per Protocol Set (PP)

All subjects in the ITT-i set without major protocol deviations that may have an impact on the efficacy analysis.

Decisions regarding which subjects are included in the per protocol set will be made before database lock on following criteria. Subjects will be included in the PP set in case:

- Subjects missed at most 3 doses in total or at most 2 consecutive doses. On the day of randomization or the next day at least one dose needs to be taken.
- The actual treatment must be the same as the planned treatment
- No unblinding may have taken place

- Subjects may not violate inclusion criteria 2,3,4 and 6 and exclusion criteria 1, 6, 9, 12 and 13.
- Influenza antiviral as part of the SOC was started no later than the day of first study drug intake,
- Subjects did not switch to another influenza antiviral as a part of the SOC

Inclusion/ Exclusion	Criterion number	Description
Inclusion	2	Tested positive for influenza A infection after the onset of symptoms, using a rapid influenza diagnostic test (RIDT) or, if available, a PCR-based or other rapid molecular diagnostic assay.
Inclusion	3	Requires hospitalization to treat influenza infection and/or to treat complications of influenza infection (eg, radiological signs of lower respiratory tract disease, septic shock, central nervous system [CNS] involvement, myositis, rhabdomyolysis, acute exacerbation of chronic kidney disease, severe dehydration, myocarditis, pericarditis, ischemic heart disease, exacerbation of underlying chronic pulmonary disease, including asthma, chronic obstructive pulmonary disease [COPD], decompensation of previously controlled diabetes mellitus), including subjects admitted to the ICU. Note: for the purpose of the protocol, subjects admitted under "observation" status with an anticipated length of stay beyond 24 hours are eligible for enrollment.
Inclusion	4	Enrollment and initiation of study drug treatment ≤96hours after onset of influenza symptoms.
Inclusion	6	Having a screening/baseline NEWS2 of ≥4.
Exclusion	1	Received more than 3 doses of influenza antiviral medication (eg, OST or zanamivir), or any dose of RBV within 2 weeks, prior to first study drug intake. Received IV peramivir more than 1 day prior to screening.
Exclusion	6	Severely immunocompromised in the opinion of the investigator (eg, known cluster of differentiation 4^+ [$CD4^+$] count <200 cells/mm^3, absolute neutrophil count <750/mm^3, first course of chemotherapy completed within 2 weeks prior to screening, history of stem cell transplant within 1 year prior to screening, history of a lung transplant).
Exclusion	9	Taken any disallowed therapies as noted in the Protocol, pre-study and concomitant therapy before the planned first dose of study drug.
Exclusion	12	Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments (eg, subject is unable to swallow medication tablets outside the hospital setting), with the exception of ePRO completion (see the protocol) ie, if a subject is not able to complete ePRO, the subject is still allowed to be enrolled in the study.
Exclusion	13	Subject has presence of any pre-existing illness, clinically significant laboratory abnormalities, ECG findings, or physical examination findings that, in the opinion of the investigator, would place the subject at an unreasonably increased risk through participation in this study. The investigator should consider the laboratory parameter criteria for study drug discontinuation when screening a subject for enrollment.

2.2.2.3. Intent-To-Treat non-infected (ITT-ni) Set

All subjects from the RAND analysis set who receive at least 1 dose of study drug and who do not have a confirmed infection with influenza A.

2.2.3. Safety Analysis Set

2.2.3.1. Safety Set or All Subjects Treated (AST)

All safety endpoints will be evaluated on the Safety population, consisting of all subjects who received at least one dose of study drug and will be analyzed by treatment arm as treated.

2.2.4. Pharmacokinetics (PK) Analysis Set

The PK analysis set is defined as subjects who have received at least 1 dose of pimodivir and have at least 1 valid blood sample drawn for PK analysis.

2.2.5. Pharmacodynamics (PD) Analysis Set

The PD analysis set is defined as all subjects in the PK analysis set for whom at least one PK parameter could be derived.

2.3. Definition of Subgroups

See Table 3 for the definitions of all the subgroups. The third column in the table indicates for which endpoints the subgroup is applied.

Descriptive statistics will be produced for the different subgroups.

In demographics and baseline disease characteristics, the following subgroups will be used:

- Region
- Influenza A subtype category
- Treatment extension
- Age group
- Time since onset of influenza symptoms (actual: ≤72 hours, >72 hours)
- Time since onset of influenza symptoms (actual: ≤48 hours, >48 - 72 hours, >72 hours)
- Type of SOC at baseline (actual)
- NEWS2 at screening (actual)
- Baseline resistance
- Any baseline polymorphism
- Influenza season
- Study Period
- COVID-19 impacted

Stratification factors (actual) will be used as subgroups for concomitant medication.

For the primary and the six most important secondary endpoints (i.e.: All endpoints included in the hierarchy testing) the subgroup with subgroup*treatment interaction term will be added in the statistical analysis models, except for the study period subgroup, where the analysis will be performed separately for each individual category of the subgroup. For further details see Section 5.2.3. and Section 5.3.2. For other endpoints, the statistical analysis will be performed separately for each individual category of the subgroup.

Table 3: Subgroups with their definition

Subgroup	Definition	Endpoints
Region	Based on country according to UN classification of Geographic regions[9]: • Europe/Africa • Northern-America • Latin America and the Caribbean • Asia and Oceania	- Efficacy (primary and secondary endpoints, excluding viral kinetics endpoints)
Age group (years)	• 13-17 years • 18-65 years • 66-85 years	- Efficacy (primary and secondary endpoints, excluding viral kinetics endpoints) - All Safety
NEWS2 at screening (actual)	• 4-5 • ≥6	- All Efficacy - Viral Phenotype - Viral Genotype
Type of SOC at baseline (actual)	• SOC including influenza antiviral treatment • SOC not including influenza antiviral treatment	- All Efficacy - Viral Phenotype - Viral Genotype - Safety(AE summary, AEs and SAEs by MedDRA system organ class and preferred term, , influenza-related complications, laboratory toxicity)
Time (hours) from onset of influenza symptoms to first study drug intake (actual)	• ≤72 hours • >72 - 96 hours	- All Efficacy - Viral Phenotype - Viral Genotype - Safety(AE summary, AEs and SAEs by MedDRA system organ class and preferred term, , influenza-related complications, laboratory toxicity)
Time (hours) from onset of influenza symptoms to first study drug intake (actual) – 3 categories	• ≤48 hours • >48 - 72 hours • >72 - 96 hours	- All Efficacy - Viral Phenotype - Viral Genotype
Influenza A subtype category	• A/H1N1 • A/H3N2 • Other	- Primary endpoint - The six most important secondary endpoints - All viral kinetics - Viral phenotype - Viral genotype
Hospitalization status	• Hospitalized • Outpatient	- Only CM TLFs
Treatment extension	• Extended treatment • No extended treatment	- All Efficacy - Viral Phenotype - Viral Genotype

Subgroup	Definition	Endpoints
Baseline polymorphism (based on influenza PB2 genotype)	Polymorphism on one or any of these amino-acid positions of interest: • Q306 • F323 • S324 • F325 • S337 • H357 • F363 • K376 • T378 • F404 • Q406 • M431 • N510	- Primary endpoint - Viral Phenotype - Viral Genotype - Viral kinetics
Baseline Resistance (Based on influenza PB2 phenotype)	Based on fold change (FC) in EC_{50} for pimodivir: • FC≤4 • FC>4	- Primary endpoint - Viral Phenotype - Viral Genotype - Viral kinetics
Influenza Season	• Northern Hemisphere 2017/2018 • Southern Hemisphere 2018 • Northern Hemisphere 2018/2019 • Southern Hemisphere 2019 • Northern Hemisphere 2019/2020 • Southern Hemisphere 2020 and so on to capture all enrolled subjects	- Efficacy (primary and the six most important secondary endpoints only) - All viral kinetics - Viral phenotype - - Viral genotype
Study period	• pre interim (subjects enrolled for the interim analysis, i.e.: randomized before or on February 28, 2020) • post interim (subjects enrolled after the interim analysis, i.e.: randomized after February 28, 2020)	-Efficacy (primary and the six most important secondary endpoints only) -safety (Safety(AE summary, AEs and SAEs by MedDRA system organ class and preferred term, , influenza-related complications, laboratory toxicity))
COVID-19 impacted	• Yes • No COVID-19 impacted is based on any COVID-19 related AEs, COVID-19 related PD, any COVID-19 related treatment or study withdrawal	-Efficacy (primary and the six most important secondary endpoints only) - Safety (AE summary, AEs and SAEs by MedDRA system organ class and preferred term, influenza-related complications, laboratory toxicity)

Subjects enrolled from 1st October 2017 to 31th March 2018 are considered to be in the Northern Hemisphere 2017/2018 category and subjects enrolled from 1st April 2018 to 30st September 2018 are considered to be in the Southern Hemisphere 2018 category. Subjects enrolled from 1st October 2018 to 31th March 2019 are considered to be in the Northern Hemisphere 2018/2019 category and subjects enrolled from 1st April 2019 to 30st September 2019 are considered to be in the Southern Hemisphere 2019 category, and so on.

Note: The six most important secondary endpoints are: incidence in post-baseline complications, time to hospital discharge, time from ICU admission to ICU discharge, time to return to daily activities, time from start of mechanical ventilation to end of mechanical ventilation, rate of re-hospitalization.

Additional subgroup analysis may be specified in a separate analysis plan and reported separately from the clinical study report.

2.4. Study Day and Relative Day

Reference date refers to the start date of the first study drug administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

The relative day (reldy) will be defined as:

reldy = visit date – reference date + 1 for visits on or after the reference date,

reldy = visit date – reference date for visits before the reference date.

Consequently there is no 'day 0' defined.

2.5. Baseline and Endpoint

The baseline analysis visit is defined as the last assessment before the first intake of the study drug, with the possible exception for height, weight, viral load results from the central lab testing and the hospital recovery scale (HRS). Height and weight are only recorded once, at screening/baseline visit, and the values recorded at this visit will be allocated to the baseline analysis visits irrespective of start of study drug For viral load, if no measurement is available prior to first dose of study drug, then the first result from the central lab testing obtained up to and including 30 minutes after first dose of study drug will be considered as the baseline assessment and will be flagged in the analysis dataset. The baseline HRS is defined irrespective of the time of the start of study drug, and is covering the screening/baseline/day 1 visit which may be performed over two days as defined per protocol. Baseline HRS will be assigned to Day 1.

As specified in the protocol, an ECG recording within 1 calendar day before signing of the ICF/assent form can be used as baseline ECG requirement, if no ECG measurement was performed between signing ICF and first study drug intake.

For programming purposes the baseline record 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 vital signs, NEWS2, ECG and central laboratory data the last study visit (Endpoint) is defined as the last scheduled study visit/timepoint and will be either the final study visit (day 28) or the safety follow-up visit.

For viral phenotyping, the last visit (Endpoint) is defined as the last study visit/timepoint for which an EC_{50} and/or IC_{50} result is available (including unscheduled visit results).

2.6. Other Definitions

For FDA marketing authorization approval in the US all subjects will be included in the analysis.

The oseltamivir subset (OST subset) contains only those subjects with oseltamivir (OST) use as part of their SOC treatment. The first dose of OST may be given before the subject was randomized but should be started no later than the day of first study drug intake.

The complete analysis will be repeated restricted to the OST subset to support marketing authorization approval in EMA.

Analyses to support authorization approval in other regions or countries, will include all subjects (depending on the enrichment of the interim analysis) unless the Health Authority of the regions or country requests otherwise and may be specified in a separate analysis plan and may also be reported separately

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analyses

An interim analyses will be performed by an independent Statistical Support Group (SSG) and will be reviewed by the Independent Data Monitoring Committee (IDMC). Only the IDMC and the SSG will be unblinded to the data. The IDMC will provide recommendations to a Sponsor Committee.

An interim analysis will be implemented to assess lack of efficacy in the subgroup with time since onset of influenza symptoms between 72 and 96 hours.

- In case lack of efficacy is concluded for the subgroup with time since onset of influenza symptoms between 72 and 96 hours:
  - Enrollment in this subgroup will be stopped
  - Sample size re-estimation will be performed based on the subgroup with time since onset of influenza symptoms ≤72 hours and consequently, the sample size of this subgroup may be increased. The maximum number of subjects that may be enrolled in this subgroup will be approximately 900.
  - Futility will be assessed in the subgroup with time since onset of influenza symptoms ≤72 hours based on re-estimated sample size.
  - At the final analysis, hypotheses will be evaluated in the subgroup with time since onset of influenza symptoms ≤72 hours.
- In case no lack of efficacy is concluded for the subgroup with time since onset of influenza symptoms between 72 and 96 hours:
  - The subgroup with time since onset of influenza symptoms between 72 and 96 hours will be continued in the study.
  - Sample size re-estimation will be performed based on all subjects. The sample size may be increased. The maximum total number of subjects that may be enrolled in the study

will be approximately 900. The study population should consist of at least 75% of subjects with first administration of study drug ≤72 hours since onset of influenza symptoms.

- Futility will be assessed in all subjects based on re-estimated sample size.
- At the final analysis, hypotheses will be evaluated in all subjects.

Details on the statistical decision rules will be provided in the IDMC SAP. The interim analysis will be conducted at the end of the first influenza season when between 300 and 450 subjects have been enrolled or during the season when 450 subjects have been enrolled. Further details will be specified in the IDMC charter.

3.2. Independent Data Monitoring Committee

An IDMC will be established to monitor data on a regular 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 details will be provided in a separate IDMC charter.

The IDMC will consist of at least 3 members, including one medical expert in the relevant therapeutic area and at least one statistician knowledgeable about statistical methods for clinical studies and sequential analysis of study data. One of these individuals will chair the Committee. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

4. SUBJECT INFORMATION

All general analyses will be done on the ITT-i Set and the Safety Set unless specified otherwise for a specific display.

4.1. Demographics and Baseline Characteristics

Demographics and baseline disease characteristics will also be done on the PP and ITT-ni sets.

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, Multiple). The specification of the category 'Multiple' will only be listed. The 'Not reported category' will not be added for the denominator.
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
  - Country
  - Geographic region (Based on country according to UN classification of Geographic regions[9]: Europe/Africa, Northern-America, Latin America and the Caribbean, Asia and Oceania)
  - Age (years and categories: 13-17 years [≥13 - <18], 18-65 years [≥18 - ≤65], 66-85 years [>65 - ≤85])
  - Age (years and categories: Adolescents (12-17 years) [≥12 - ≤17], Adults (18-64 years) [≥18 - ≤64], From 65 to 84 years [≥65 - ≤84], 85 years and over [≥85])
  - 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)
  - Current Tobacco use: tobacco, cigarettes, cigars, patches/gum, pipes, E-cigarettes or equivalent, smokeless tobacco (Yes, No, Missing). Note that 'No' also includes ex-smokers.
  - Childbearing potential (only listed)

- Baseline disease characteristics:
  - Influenza A subtype category (A/H1N1, A/H3N2, No subtype)
  - Baseline influenza A viral load (log_{10} vp/mL), assessed by qRT-PCR
  - Baseline influenza A viral titer (log_{10} $TCID_{50}$/mL) assessed by viral culture

- qRT-PCR negativity at baseline
- Viral culture negativity at baseline
- Broad respiratory panel (show the reported pathogen)
- Return to daily activities at baseline
- Patient Global Impression of Severity of Influenza symptoms at baseline
- EQ-5D VAS at baseline
- EQ-5D Valuation index at baseline
- NEW2 Score at screening (4-5, >=6), as randomized
- NEW2 Score at screening (4-5, >=6), actual
- Hospital recovery scale category at baseline
- Fundamental hospital recovery scale category at baseline
- Respiration rate at baseline (breaths/min)
- Arterial oxygen saturation at baseline on room air (%)
- Arterial oxygen saturation at baseline overall (%)
- Supplemental oxygen at baseline (yes, no) (following supplemental oxygen types are considered: nasal cannula, venturi mask, simple face mask and nonrebreathing face mask with reservoir and one way valve)
- Mechanical ventilation use at baseline (yes, no)
- Temperature (°C) at baseline
- Systolic blood pressure at baseline (mmHg)
- Heart rate at baseline (beats/min)
- Level of consciousness at baseline
- Time since onset of influenza symptoms as randomized (≤72, >72 hours),
- Time since onset of influenza symptoms, actual time (hours) [the actual time will be calculated from start date and time of acute respiratory symptoms until datetime of first study drug intake, if the time is missing, the midpoint of the time interval as recorded per CRF will be used.]
- Time since onset of influenza symptoms, actual (≤72, >72 hours)
- Time since onset of influenza symptoms, actual – 3 categories (≤48, >48 – 72h, >72 hours)
- Type of SOC at baseline, as randomized (including or not including influenza antiviral treatment)
- Type of SOC at baseline, actual (including or not including influenza antiviral treatment), for the SOC including antiviral treatment the influenza antiviral will also be shown

- SOC including oseltamivir (yes, no)
- Chronic oxygen use(yes, no)
- Primary reason for hospitalization at baseline (prioritize influenza in case >=2 reasons are selected, then adverse event and then medical history)
- Type of influenza A diagnostic assay (Rapid antigen-based diagnostic test, Rapid molecular diagnostic test)
- In ICU at baseline (yes, no)
- Baseline resistance
- Any baseline polymorphism

4.2. Disposition Information

Summaries will be provided for the following disposition information:

- Number of subjects screened, screening failures, randomized, randomized and not treated, randomized and/or treated, randomized and treated, randomized and no confirmed Influenza A, ITT-i set, ITT-ni set, per protocol set, and safety set. The planned treatment arm will be shown, except for the randomized and/or treated and safety sets where the actual treatment will be shown. The number (%) of subjects impacted by the COVID-19 pandemic will be presented for the ITT-i, ITT-ni, per protocol and safety analysis sets.
- Number of subjects who completed/discontinued treatment and/or the trial, with the reasons of discontinuation. The number of subjects that discontinued due to an AE that is related to COVID-19 and that discontinued due to another reason related to COVID -19 will be added.
- Kaplan-Meier curves of the time to completion or discontinuation (in days) of the treatment/trial per treatment group, overall and separately for subjects with/ without treatment extension. Note at the final analysis all subjects will have the event of completion or discontinuation and no subjects will be censored.
- Number of subjects with a visit at each scheduled analysis timepoint by phase and the missing visits and visits different from planned due to COVID-19 per phase.
- Number of subjects enrolled per month, quarter, season and year.

4.3. Treatment Compliance

Treatment compliance for pimodivir/placebo 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 drug accountability information (DA domain) as the amount of drug dispensed minus the returned amount (in case both amounts are known, otherwise treatment compliance will be missing)

To differentiate between the compliance during the planned treatment subperiod and the planned treatment extension subperiod, the date of dispensing the tablets will be compared with the treatment extension start date (DS Domain). If the drug is dispensed before the treatment extension

start date it will be used for the compliance of the treatment subperiod. If the drug is dispensed on or after the treatment extension start date the amount will be used for the compliance of the treatment extension subperiod.

For placebo or pimodivir the actual number of doses needs to be divided by 2 as the study uses 300 mg tablets. For subjects without treatment extension the planned number of study drug is 20 tablets of placebo or pimodivir hence the planned number of doses per study drug equals 10 doses. For subjects with treatment extension the planned dose is doubled. Note that the planned number of doses is irrespective of whether the subject discontinued during the treatment phase.

Dosing compliance will be summarized descriptively in the treatment phase and per subperiod and by discontinuing the trial during the treatment period (Yes, No).

4.4. Extent of Exposure

The extent of exposure (hours) is defined as datetime of last study drug intake – datetime of first study drug intake + 12 hours. Note: treatment interruptions will not be taken into account.

Extent of exposure will be summarized descriptively in the treatment phase, overall and by treatment subperiod.

A listing will be made to present the exposure to study drug for subjects impacted by COVID-19 (based on reason ‘Other’ containing ‘COVID’).

4.5. Protocol Deviations

The number and percentage of subjects with major protocol deviations will be tabulated overall and per coded major protocol deviation.

A listing will be made of all major protocol deviations for the subjects in the safety set.

Additionally, a listing of major and separately a listing for minor protocol deviations related to COVID-19 will be made.

Additionally, for subjects in the ITT-i set, the number and percentage of subjects with a reason for exclusion from the per protocol set will be tabulated overall and for each reason for exclusion.(see Section 2.2.2.2).

A listing will also be made of all reasons for exclusion from the per protocol set for subjects in the ITT-i set.

4.6. Prior and Concomitant Medications

Medications reported from 7 days before first dose of study drug and up to last contact date will be summarized by preferred term using the World Health Organization-Drug Dictionary for the ITT-i 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, type of SOC, corticosteroids, and medication administered to treat COVID-19 infection by ATC class and by hospitalization status. Additionally, tabulations will be made of concomitant corticosteroids and antibiotics administered because of adverse events reported as influenza complications.

The ATC level 2 code J01 will be used to identify concomitant antibiotics.

The ATC level 2 code H02 and the ATC level 4 codes M01BA, R03BA, and R03AK will be used for identifying corticosteroids. Separate frequency tabulations will be made for antipyretic medication and oxygen supplementation. The ATC level 4 codes N02BA and N02BE and the generic medication names paracetamol, ibuprofen, and acetylsalicylic acid will be used to identify antipyretic medications. The table showing oxygen supplementation will be tabulated per analysis visit, phase and treatment subperiod. 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 datetimes, 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.

4.7. Medical history

The influenza vaccination status will be tabulated by:

- Vaccinated in previous season, not in current season
- Vaccinated in current season, not in previous season
- Vaccinated in previous and current season.
- Not vaccinated in previous and current season

The use of antiviral influenza medication prior to study drug initiation will be tabulated separately.

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

Other medical history will be tabulated by subcategory and/or will be listed.

5. EFFICACY

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and stratification factors (NEWS2 at screening, baseline SOC and time since onset of symptoms). For the analyses restricted to subjects who received OST as part of their SOC, type of baseline SOC will not be included as a stratification factor or model parameter.

5.1. Analysis Specifications

5.1.1. Level of Significance

The population used for the evaluation at the final analysis will depend on the outcome scenario of the interim analysis: i.e.; scenario 1: continue with the full study population or scenario 2: continue only with the subjects with an onset of symptoms less than 72 hours before first study drug intake. Tables/graphs/listings will account for the selected scenario.

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, in either scenario, a combination of hierarchical testing and the Bonferroni-Holm testing procedure will be applied to control for the overall Type I error rate at the 5% level. The following endpoints are included in the confirmatory strategy:

1. Hospital recovery scale at Day 6, ie, primary endpoint
2. Incidence in post-baseline complications
3. Time to hospital discharge
4. Time from ICU admission to ICU discharge
5. Time to return to daily activities
6. Time from start of mechanical ventilation to end of mechanical ventilation
7. Rate of re-hospitalization

First, the primary endpoint will be tested for superiority of pimodivir in combination with SOC over placebo in combination with SOC at the 2-sided 5% significance level.

The confirmatory test procedure follows the Serial Gate Keeping strategy as outlined in Section 7 of the FDA's draft guidance on Multiple Endpoints to control the overall type I error at the 5% 2-sided level. The primary and six most important secondary endpoints (listed above) will be tested in the hierarchical order per the 5 steps outlined below. All alphas and p-values specified are 2-sided.

Step 1: Test the primary hypothesis ("Hospital recovery scale at Day 6")

- If the p-value is ≤5%, continue to Step 2.
- If the p-value is >5%, stop testing, and no claim will be made.

Step 2: Test first set of 2 secondary endpoints ("Incidence in post-baseline complications" and "Time from start of study drug to hospital discharge"). The Bonferroni-Holm procedure will be applied to control the type I error within Step 2.

- If the smallest of the 2 p-values is ≤2.5% and the largest of the 2 p-values is ≤5%, continue to Step 3.
- If the p-value for "Incidence in post-baseline complications" is ≤2.5% but the p-value for "Time from start of study drug to hospital discharge" is >5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6" and "Incidence in post-baseline complications".
- If the p-value for "Time from start of study drug to hospital discharge" is ≤2.5% but the p-value for "Incidence in post-baseline complications" is >5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6" and "Time from start of study drug to hospital discharge".
- If the smallest of the 2 p-values is >2.5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6" only.

Step 3: Test second set of 2 secondary endpoints ("Time from ICU admission to ICU discharge" and "Time to return to daily activities"). The Bonferroni-Holm procedure will be applied within Step 3.

- If the smallest of the 2 p-values is ≤2.5% and the largest of the 2 p-values is ≤5%, continue to Step 4.
- If the p-value for "Time from ICU admission to ICU discharge" is ≤2.5% but the pvalue for "Time to return to daily activities" is >5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6", "Incidence in post-baseline complications", "Time from start of study drug to hospital discharge" and "Time from ICU admission to ICU discharge".
- If the p-value for "Time to return to daily activities" is ≤2.5% but the p-value for "Time from ICU admission to ICU discharge" is >5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6", "Incidence in postbaseline complications", "Time from start of study drug to hospital discharge" and "Time to return to daily activities".
- If the smallest of the 2 p-values is >2.5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6", "Incidence in postbaseline complications" and "Time from start of study drug to hospital discharge".

Step 4: Test the fifth secondary endpoint ("Time from start to end of mechanical ventilation")

- If the p-value is ≤5%, continue to Step 6.
- If the p-value is >5%, stop further testing of the secondary endpoints, and make a claim on "Hospital recovery scale at Day 6", "Incidence in post-baseline complications", "Time from start of study drug to hospital discharge", "Time from ICU admission to ICU discharge", and "Time to return to daily activities".

Step 5: Test the sixth secondary endpoint ("Rate of re-hospitalization")

- If the p-value is ≤5%, make a claim on "Hospital recovery scale at Day 6", "Incidence in post-baseline complications", "Time from start of study drug to hospital discharge", "Time

from ICU admission to ICU discharge", "Time to return to daily activities", "Time from start to end of mechanical ventilation", and "Rate of re-hospitalization".

- If the p-value is >5%, make a claim on "Hospital recovery scale at Day 6", "Incidence in post-baseline complications", "Time from start of study drug to hospital discharge", "Time from ICU admission to ICU discharge", "Time to return to daily activities", and "Time from start to end of mechanical ventilation".

For the primary endpoint, the results from the proportional odds model will be used in the hypothesis testing. If the proportional odds assumption would not hold on the treatment effect, the p-value from the van Elteren test will be used. For the secondary endpoints time from start of study drug to hospital discharge, time from ICU admission to ICU discharge, time to return to daily activities, and time from start to end of mechanical ventilation, the results of the Gehan-Wilcoxon test will be used in the hypothesis testing. For incidence in post-baseline complications and rate of re-hospitalization the results of the logistic regression will be used. For all these evaluations p-value combination tests will be used, as described below.

The final analysis on the ITT-i set (to support FDA marketing approval) and the final analysis on the OST subset (to support marketing authorization approval in EMA) will be performed independently, using a 5% two-sided significance level for each.

5.1.2. Statistical Methodology for Evaluation at the Final Analysis

All p-values below are one-sided p-values, to evaluate rejection of the null hypothesis that pimodivir is not better than placebo.

Scenario 1: The final analysis will be performed in the subgroup with time between onset of symptoms and start of treatment between 0 and 72 hours only. P-values for the final analysis will be based on 2 inverse-normal combination tests of p-values as outlined below.

Let:

p	=	p-value (one-sided) from full study population of the pre-interim' category of the study period subgroup
p_1	=	p-value (one-sided) from subgroup with time between onset of symptoms and start treatment between 0 and 72 hours of the pre-interim' category of the study period subgroup
p_2	=	$2*\min(p,p_1)$
q_1	=	p-value (one-sided), from subgroup with time between onset of symptoms and start treatment between 0 and 72 hours on the patients enrolled of the 'post-interim' category of the study period subgroup
N_1	=	actual sample size at interim i.e.:all randomized subjects analysis set (RAND) included in the IA
N	=	600, the initially planned study sample size
w_1	=	$\text{sqrt}(N_1/N)$
w_2	=	$\text{sqrt}(1-(N_1/N))$
$\varphi^{-1}(x)$	=	the inverse of the standard normal cumulative distribution function in x

Note: p_1 and q_1 are based on a subset of subjects with onset of symptoms and start treatment between 0 and 72 hours, and therefore this stratification factor is not included in the respective models.

The p-values resulting from the following 2 combination tests both should be below the pre-specified alpha (2.5% one-sided) to claim superiority in subgroup with time between onset of symptoms and start of treatment between 0 and 72 hours:

$1-\varphi(C(p_1,q_1))$ where $C(p_1,q_1) = w_1 * \varphi^{-1}(1-p_1) + w_2 * \varphi^{-1}(1-q_1)$

$1-\varphi(C(p_2,q_1))$ where $C(p_2,q_1) = w_1 * \varphi^{-1}(1-p_2) + w_2 * \varphi^{-1}(1-q_1)$

Scenario 2: The final analysis will be performed in the full study population. P-values for the final analysis will be based on 2 inverse-normal combination tests of p-values.

Let additionally:

q	=	p-value from full study population on the patients enrolled of the 'post-interim' category of the study period subgroup

The p-values resulting from the following 2 combination tests both should be below the pre-specified alpha to claim superiority in the full study population:

$1-\varphi(C(p,q))$ where $C(p,q) = w_1 * \varphi^{-1}(1-p) + w_2 * \varphi^{-1}(1-q)$

$1-\varphi(C(p_2,q))$ where $C(p_2,q) = w_1 * \varphi^{-1}(1-p_2) + w_2 * \varphi^{-1}(1-q)$

5.1.3. Data Handling Rules

For analysis purposes the $\log_{10}$ qRT-PCR viral load will be imputed with 2.12 when the result is 'TARGET DETECTED' (.i.e. below the limit of quantification: <2.18) and with 2.05 if result is

'TARGET NOT DETECTED' (i.e. below limit of detection: <2.05). The log_{10} $TCID_{50}$ viral titer will be imputed with 0.74 when the result is '<0.75' (below limit of quantification).

5.1.4. Stratification Factors

The actual values of the stratification factors will be used for all analyses.

The concomitant medications indicated as standard-of-care treatment on the concomitant medication form will be used for determining the actual strata for type of baseline SOC. If no influenza antiviral is recorded it will be assumed that the subject received SOC not including influenza antiviral. The following ATC level 4 code and generic medication names indicate an influenza antiviral:

- J05AH (including neuraminidase inhibitors)
- Laninamivir
- Umifenovir
- Amantadine
- Rimantadine
- Ribavirin
- Baloxavir Marboxil

The datetime when first acute respiratory symptoms appeared and the datetime of first dose of study drug will be used for determining the actual strata for time since symptom onset relative to treatment initiation.

The actual NEWS2 will be calculated as explained in Section 7.6. Note that a subject is considered to receive supplemental oxygen if the subject received oxygen according to the CM dataset at least at one point between 15 min before randomization date time to the randomization date time.

When an incorrect stratification occurred for the NEWS(2) such that the actual NEWS2 is lower than 4 or for the time to onset of symptoms to first study drug intake (i.e.: >96 hours) then use the randomized stratification category instead. Similarly, in case of missing data to calculate the actual NEWS2 stratification the randomized stratification factor will be used, except if the NEWS2 is greater or equal to 6 based on the available non-missing parameters, then the actual stratification will be '6 or more'.

There will be no missing stratification factors values for randomized subjects receiving study drug.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The primary efficacy analysis will be based on the ITT-i analysis set and consists of the analysis of the hospital recovery scale outcome on Day 6.

The hospital recovery scale provides 6 mutually exclusive conditions ordered from best to worst, and the score reflects the subject's worst situation on the day of assessment:

1. Not hospitalized
2. Non-ICU hospitalization, not requiring supplemental oxygen
3. Non-ICU hospitalization, requiring supplemental oxygen
4. Admitted to the ICU, not requiring invasive mechanical ventilation
5. Requiring invasive mechanical ventilation
6. Death

The hospital recovery scale categories are defined below. For ease of categorization, the categories are defined from worst to best. A subject will be evaluated in the same ordering of the categories as below. Once a subject fulfils the criteria for a category, the category is assigned to the subject and the evaluation stops.

6. Death
   - Subject died at any time on the day of assessment or earlier (all-cause mortality).

5. Requiring invasive mechanical ventilation
   - Any oxygen support requiring intubation or extracorporeal oxygenation
   - Invasive mechanical ventilation is used at any time on the day of assessment.

4. Admitted to the ICU, not requiring invasive mechanical ventilation

   Subject met either of the 2 following criteria:

   - In the ICU (and ICU level of care is required during the day of assessment)
   - On the hospital ward, with or without supplemental oxygen, but deemed to require ICU level of care at any time during the day of assessment (e.g., not transferred to ICU due to bed availability)

     Requiring ICU level of care is defined by:

     - Some specific conditions:
       - Treatment of acute unstable arrhythmias
       - Treatment of complicated acid-base or electrolyte imbalances
       - Large volume resuscitation
       - Utilization of intravenous vasoactive medications
       - S/P cardiac arrest
       - Cardiogenic Shock
       - Acute myocardial infarct with complications
       - Cardiac tamponade
       - Acute congestive heart failure
       - Acute or imminent respiratory failure
       - Hemodynamic instability

  - Diabetic ketoacidosis complicated by hemodynamic instability, altered mental status, respiratory insufficiency, or severe acidosis

- Other conditions requiring specialized equipment and/or staff competencies only available in the ICU

3. Non-ICU hospitalization, requiring supplemental oxygen

   Subject met either of the 2 following criteria:

   - Non-ICU hospitalized on the day of assessment (including readmittance), not ready for discharge during the whole day of assessment, as judged by the investigator and supplemental oxygen is required by the subject
   - In the ICU but there is no medical reason to be in the ICU during the day of assessment, and supplemental oxygen is required by the subject

   Requiring supplemental oxygen is defined by:

   - Receiving supplemental oxygen through a face mask or nasal cannula and not being able to sustain a blood oxygen saturation of ≥94% when breathing room air for 15 minutes at any time on the day of assessment.
   - If supplemental oxygen was provided chronically pre-influenza infection (based on medical history), that amount of supplemental oxygen is exceeded to prevent hypoxia, tachypnea or dyspnea at some point on the day of assessment.
   - Not receiving supplemental oxygen and either:
     - Having a blood oxygen saturation of <94% when breathing room air for 15 minutes at any measurement on the day of assessment, or
     - In case of known pre-influenza SpO_2 <94% (e.g., due to COPD), the current blood oxygen saturation on room air is lower than pre-influenza infection levels by at least 3%.

2. Non-ICU hospitalization, not requiring supplemental oxygen

   Subject met either of the 2 following criteria:

   - Non-ICU hospitalized on the day of assessment (including readmittance) and not ready for discharge during the whole day of assessment, as judged by the investigator
   - In the ICU but there is no medical reason to be in the ICU during the day of assessment

1. Not hospitalized

   Any of the following:

   - Discharged from the hospital before the day of assessment
   - Hospitalized at the day of assessment but ready for discharge on both the day of assessment and the day prior, as judged by the investigator (e.g., in case of lack of bed availability in a skilled nursing facility, lack of social support at home).

Notes: If a subject was discharged from the hospital "Against Medical Advice" on the day prior to the day of assessment, the subject will be considered as hospitalized (evaluating the other aspects of the HRS to define the correct category based on available data, e.g.: requiring supplemental oxygen, on the day of assessment). The hospital recovery scale category will be considered missing on subsequent days.

The HRS will be missing after a subject withdrew (except for withdrawal due to death) from the study.

See Attachment 6 for details of the derivation of the HRS categories.

5.2.2. Estimand

The population of interest is hospitalized subjects between 13 to 85 years old with a confirmed influenza A infection.

The primary variable is the hospital recovery scale as assessed on Day 6 and will be compared between pimodivir and placebo on top of SOC. The hospital recovery scale is an ordinal mutually exclusive scale of six categories (death, requiring mechanical ventilation, requiring ICU, non-ICU hospitalized requiring supplemental oxygen, non-ICU hospitalized not requiring supplemental oxygen and non-hospitalized).

The intercurrent event of the use of influenza antivirals as part of SOC is handled in a treatment policy strategy as the primary endpoint is derived in the same way irrespective of the components of SOC. Treatment discontinuation is an intercurrent event that is also handled in a treatment policy strategy. Death as intercurrent event is handled in a composite strategy as it is one of the categories of the HRS. Other factors as for example bed availability that can influence the status of the subject are intercurrent events that are also handled with the composite strategy as the HRS accounts for the status of where the subject 'should be' instead of where the subject physically is.

The common odds ratio estimated by a proportional odds model is used as the population-level summary. If the assumption (by testing the parallel slopes for the treatment effect only) of the proportional odds would not hold for the treatment effect, the Van Elteren test will be used in a sensitivity analysis and the resulting p-value would be used in the formal testing. A second sensitivity analysis is conducted to handle missing data by an MAR/MNAR multiple imputations method. This is done for all missing HRS values on day 6 and separately for HRS values on day 6 that are missing due to COVID-19 and for HRS values that are missing not due to COVID-19.

5.2.3. Analysis Methods

A proportional odds model will be used as primary model to analyze the hospital recovery scale on Day 6, modeling the common odds ratio of improvement on the ordinal scale of active treatment versus placebo. The model will include treatment, hospital recovery scale category at baseline and the stratification factors (NEWS2 category at screening, type of baseline SOC, and time since onset of influenza symptoms). In a first step equal slopes (i.e. proportional odds) for the treatment effect only and unequal slopes for the other covariates, will be modeled. If this model does not fit a full

proportional odds model will be applied, i.e. implying proportional odds for all covariates in the model. The common odds ratio from the final model will be considered as the estimate of the treatment effect. The actual values of the stratification factors will be used for all models, not as randomized. The proportional odds model will be defined in such a way that a common odds ratio smaller than 1 indicates larger improvement in the pimodivir treatment group.

Graphical displays and tabulations will be provided showing the proportion of subjects per hospital recovery scale category and day. Also, shift tabulations will be provided of the baseline hospital recovery scale category versus the post-baseline hospital recovery scale category, per day.

The proportional odds assumption will be assessed by testing for parallel slopes for the treatment effect only.

In addition, each of 5 dichotomizations of the hospital recovery scale, ie,

- Not hospitalized, vs worse (ie, hospitalized)
- Non-ICU hospitalized without supplemental oxygen (or better), vs worse
- Non-ICU hospitalized with supplemental oxygen (or better), vs worse
- In the ICU without invasive mechanical ventilation (or better), vs worse
- Invasive mechanical ventilation (or better), vs worse (ie, died)

will be analyzed using a logistic regression model, including treatment, hospital recovery scale category at baseline and stratification factors.

The hospital recovery scale will also be analyzed using the Van Elteren test with strata defined by the stratification factors[3, 6].

A table will be created showing the number (%) missing HRS values at day 6 overall and by reason: study discontinuation: due to COVID-19 and not due to COVID-19, discharged against medical advice prior to day 5 and subjects that have no confirmed influenza A.

In case of more than 10% missing data on Day 6: multiple imputation will be employed as sensitivity analyses for the proportional odds model of the HRS (excluding the subgroup analyses), under the missing-at-random (MAR) assumption and missing-not-at-random (NMAR) assumption.

- If more than 5% of the patients have a missing HRS value due to COVID-19 (i.e.: discontinued due to COVID-19), the multiple imputation method will also be done separately on these subjects.
- If more than 5% of the patients have a missing HRS values unrelated to COVID-19, then also multiple imputation will be done separately in this group.

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 14). The number of imputation datasets will be the same as the percentage of missing data[10]. For MAR assumptions, a monotone ordinal logistic regression imputation model will be used to complete the remaining missing clinical outcomes.

For the NMAR assumption, the imputed datasets obtained from the MAR assumption described above will be used, but with a structural shift in hospital recovery scale category on Day 6 of the imputed values, to introduce non-ignorable missing patterns:

- To reflect missingness patterns as a result of study discontinuation due to a dissatisfying treatment effect or safety issues in the placebo treatment group, the following shifts will be applied in the placebo treatment group only:
    - 1 category down, eg, from '1. Not hospitalized' to '2. Non-ICU hospitalization, not requiring supplemental oxygen'
    - 2 categories down, eg, from '1. Not hospitalized' to '3. Non-ICU hospitalization, requiring supplemental oxygen'
- To reflect missingness patterns as a result of study discontinuation due to a dissatisfying treatment effect or safety issues in the pimodivir treatment group, the following shifts will be applied in the pimodivir treatment group only:
    - 1 category down, eg, from '1. Not hospitalized' to '2. Non-ICU hospitalization, not requiring supplemental oxygen'
    - 2 categories down, eg, from '1. Not hospitalized' to '3. Non-ICU hospitalization, requiring supplemental oxygen'

In all cases, '6. Death' will be the worst hospital recovery scale category after imputation and structural shift and '1 Not hospitalized' will be the best hospital recovery category after imputation and structural shift.

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.

The analyses on the primary endpoint will be repeated by subgroups for efficacy as defined in Section 2.3. The final model above will be repeated adding these subgroups (defined in Section 2.3) as an additional covariate and interaction with treatment. Per subgroup the common odds ratio and the odds ratios calculated for the dichotomizations will be derived from these models. In addition, for each category in a subgroup, the Van Elteren test with strata defined by the stratification factors will be repeated.

5.3. Major Secondary Endpoints

5.3.1. Definition

Formulae to be used for derived variables, including data conversions, are provided in the tables below.

Note that for time-to event variables the actual date or times that the endpoint is met will be used. For the time-to-event variables, in case of death prior to the event, the subject will be censored using a time-to equal to the maximum time across all subjects.

5.3.1.1. Clinical Outcome

Measurement	**Formula**
Time to hospital discharge (hours) [Time-to event]	The time from first study drug intake to first hospital discharge (=event) in hours. Note this excludes time in hospital because of re-hospitalization (a new hospitalization is considered as a re-hospitalization if there is at least 1 day in between the start date of the new hospitalization and the end date of the previous hospitalization) and hospitalizations that ended before first intake. Subjects who complete or withdraw from the study while still hospitalized will be censored at the date of completion or withdrawal. If the time is not available they will be censored at 23:59. If time of end of hospitalization is not known but we have a date of discharge then time will be imputed at 23:59. (Date and time of event or censoring–- date and time of first dose of study drug)/3600, rounded to one decimal.
Time to readiness for hospital discharge (days) [Time-to event]	The time from first study drug intake until the time to readiness for hospital discharge (= event) in days, with readiness for hospital discharge defined by the investigator. In case at the date of discharge the subject is not ready to be discharged as per investigator assessment, the discharge readiness day will be set to the next day. Censoring of the time will be done analogous to "Time to hospital discharge", only using the date information, as time is not available for the event.
Total length of hospital stay (hours) [Duration]	The total number of hours a subject stayed in the hospital during the period from first study drug intake until study termination, calculated as sum of [(end date and time of hospitalization–- start date and time of first intake)/3600], rounded to one decimal for all separate hospital stays per subject. If the time is not available it will be put at 23:59 If hospitalization started before first study drug intake, then datetime of first study drug will be used. If hospitalization is still ongoing at study end, the end date and time will be imputed by the end date and time of the last phase as defined in table 1.

ICU admission started post-baseline	Incidence of post-baseline ICU admission - Admitted to ICU post-baseline - Not admitted to ICU post-baseline Note: In case a patient is in the ICU at baseline and (after discharge from the ICU) the patient is re-admitted post-baseline, this subject will be counted as ‘'Admitted to ICU post-baseline’'.
First admission to intensive care unit (ICU)	When was the subject first admitted to the ICU during the study? Categories: - In ICU at baseline - Admitted in ICU Post-baseline - Never admitted to ICU
Time from ICU admission to ICU discharge (hours) [Time-to event]	The time from max(first admission to ICU, first study drug intake) until the time of first discharge from the ICU. Censoring and calculation of the time will be done analogous to “Time to hospital discharge”. Only subjects admitted to the ICU (at any point during the trial) are included in the analysis and analysis is restricted to the first ICU admission.
Time from ICU admission requiredness to ICU discharge readiness (days) [Time-to event]	The date from max(requiring ICU level of care , first study drug intake) until the date of not requiring ICU anymore(= event), requiring ICU level of care to be defined by the investigator. Censoring and calculation of the time (days) will be done analogous to “Time to hospital discharge” Subjects that do not require ICU level of care will be excluded from this analysis and this analysis is restricted to the first required ICU level of care.

Total time in intensive care unit (ICU) stay (hours) [Duration]	The total number of hours a subject stayed in ICU during the period from first intake until study termination, calculated as sum of [(end date and time of discharge–- start date and time of admission)/3600], rounded to one decimal for all separate events per subject In case ICU admission took place before first intake or in case the start datetime of ICU is missing, then the date and time of first intake will be used. In case the ICU stay ended after the end of the trial or in case the end datetime of ICU stay is missing, then the end datetime of last contact date will be used. If time of the start of ICU admission is missing then use 00:00. If time of the end of ICU admission is missing then use 23:59. The derivation of total time in ICU is analogous to "total length of hospital stay".
Type of supplemental oxygen administration	Tabulation will be done as collected per CRF page "Oxygen Supplementation". In addition, the following categorization will be done: - Invasive Mechanical Ventilation - Non-Invasive Mechanical Ventilation - Non-Invasive, Non-mechanical Ventilation - None
Mechanical ventilation during study	Incidence of mechanical ventilation (invasive or non-invasive) Categories: - Mechanical ventilation at baseline - First administration of mechanical ventilation post-baseline - No administration of mechanical ventilation
Mechanical ventilation started post-baseline	Incidence of post-baseline mechanical ventilation (invasive or non-invasive) - Started post-baseline - Not started post-baseline Note: In case mechanical ventilation is present at baseline and a second episode of mechanical ventilation is initiated post-baseline, this subject will be counted as started post-baseline.

Time from start of mechanical ventilation to end of mechanical ventilation (hours) [Time-to event]	The time from max(start date and time of first mechanical ventilation, study drug intake) until the end date and time of mechanical ventilation. Note: Invasive and non-invasive mechanical ventilation are considered and are defined on the Oxygen Supplementation form: Type of supplemental oxygen administration. Only the first mechanical ventilation period is considered. Censoring and calculation of the end time will be done analogous to "Time to hospital discharge" if time part of the start of mechanical ventilation is missing then it will be imputed with 00:00. Subjects that are not on mechanical ventilation (at any point during the trial) are excluded from this analysis and this analysis is restricted to the first time mechanical ventilation is used.
Total time on mechanical ventilation (hours) [Duration]	The total number of hours of mechanical ventilation during the period from first intake until study termination, calculated as sum of [(end date and time of mechanical ventilation–- start date and time of mechanical ventilation)/3600], rounded to one decimal for all separate events per subject In case mechanical ventilation was started before first intake or in case the start datetime of mechanical ventilation is missing, then the date and time of first intake will be used. In case mechanical ventilation ended after the end of the trial or in case the end datetime of mechanical ventilation is missing, then the end datetime of last contact date will be used. If time of the start of mechanical ventilation is missing, then use 00:00. If time of the end of mechanical ventilation is missing, then use 23:59. The derivation of the total time is analogous to "Total length of hospital stay".
Time to clinical response (hours) [Time-to event]	The time to clinical response is defined as the time (in hours) from first study drug intake until the first assessment (actual date and time) of a successive series of 4 recordings (over 5 scheduled successive analysis timepoints, 1 missing timepoint is allowed) where at least 4 of 5 symptoms (temperature, blood oxygen saturation, heart rate, SBP, respiration rate) are normalized, with at least normalization of temperature and blood oxygen saturation. Normalization of clinical response is defined in Table 4.

	Only vital signs assessments performed during hospitalization (excluding measurements during re-hospitalization) and up to Day 14 (during hospitalization) or Day 19 (for subjects with extended treatment during hospitalization) will be taken into account to determine time to clinical response. Assessments taken after hospital discharge or after Day 14 or Day 19 (for subjects with extended treatment), 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 case clinical response is not met, data will be censored. Censoring will be done as follows 1) Last non-missing record in the applicable period indicate normalization (but insufficient recordings to meet the time to clinical response criteria) Censoring will be done at the first record of normalization 2) Last non-missing record in applicable period does not indicate normalization Censoring will be 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). When not all parameters are available on a certain timepoint then following rules apply: - If temperature or oxygen saturation are available but not normalized then there is no resolution for this timepoint - If more than 2 parameters are not normalized then there is no resolution for this timepoint - If 4 parameters including temperature and oxygen saturation are normalized (allowing 1 missing parameter) then there is resolution for this timepoint. Else the resolution on this timepoint is missing Subjects without postbaseline data are excluded.

Within 1 timepoint the assessments of the different parameters are taken together for evaluating the clinical response and the time of the last record within that time point is used. Unscheduled assessments are not taken into account. When multiple assessments for 1 parameter occur within one timepoint then only the last is used for that parameter.

Table 4: Resolution Criteria for Vital Signs

Assessment	Resolution Criterion
Temperature	Oral temperature ≤ 37.0 °C (without the use of antipyretics within 8 hours)*[1]
Oxygen saturation	a) ≥ 94% on room air without supplemental oxygen*[2] b) In case pre-influenza infection oxygen saturation <94%*[3]: Return to pre-influenza oxygen saturation*[4]
Respiration rate	≤ 24/min or return to pre-influenza infection oxygen requirement in patients with chronic oxygen use*[4,5]
Heart rate	≤ 100/min
Systolic blood pressure	≥ 90 mmHg (without inotropic support given within 2 hours of assessment) *[6]

*[1]Based on the Vital Signs form, question“"Were there any antipyretic medications given within 8 hours before temperature measurement”"
*[2]Based on the oxygen saturation level measured on room air and “YES” on the question ‘Is the patient able to sustain a blood oxygen saturation >= 94% when breathing room air for 15 min at any time on the day of assessment?’ on the vital signs form.
*[3] If pre-influenza oxygen saturation level is below 94% and measured on room air
*[4]Return to pre-influenza infection oxygen requirement is based on the oxygen supplementation form: “Has supplemental oxygen administration returned to that level provided prior to the current respiratory infection?”
*[5]Chronic oxygen use is based on the question “Does the subject require chronic oxygen”
*[6] Inotropic support given within 2 hours of assessment as recorded in the vital signs form.

Time to respiratory response (hours) [Time-to event]	Time respiratory response is defined as the time (in hours) from first study drug intake until the first assessment (actual date and time) of a successive series of 4 recordings (over 5 scheduled successive analysis timepoints, 1 missing timepoint is allowed) where the resolution criteria of both blood oxygen saturation and respiration rate as specified in Table 4 are met. Censoring and calculation of the time will be done analogous to “Time to clinical response”. In case 1 of the parameters is missing and the available parameter is not normalized then there is no resolution on this timepoint. In the other cases where 1 or 2 parameters are missing, the resolution will be also missing.

Incidence of treatment-emergent adjudicated influenza complications	The incidence of treatment-emergent adjudicated influenza complications from first study drug intake until the end of the study will be categorized in a hierarchical fashion. The incidence will be presented for the overall category, for the subcategories and for each adjudicated complication within a subcategory. The overall category will consist of any adjudicated complication. The following subcategories are defined: • Pulmonary complications: o respiratory failure, o primary viral pneumonia, o secondary bacterial pneumonia, o exacerbations of chronic underlying pulmonary diseases, o bronchitis o other complications • Extrapulmonary complications: o Cardiovascular and cerebrovascular disease (eg, myocardial infarction, congestive heart failure, arrhythmia, stroke), o Muscular disorders (eg, myositis, rhabdomyolysis), o Central nervous system (CNS) involvement, o Acute exacerbation of chronic kidney disease, o Decompensation of previously controlled diabetes mellitus, o Other infections (eg, sinusitis, otitis) o Other complications • Pulmonary complications including sinusitis and otitis • Major / minor complications • Infectious / non-infectious complications The complications sinusitis and otitis are determined based on their MedDRA preferred terms as listed in Attachment 1, table 6, for the protocol terms 'Sinus infection' and 'ear infection' respectively. Only if those terms are judged to be complications by the adjudication committee they will be included for the endpoint 'Pulmonary complications including sinusitis and otitis.
Incidence of not being hospitalized on Day 6.	On Day 6 (relative day) subject is in the hospital at least a part of the day ('Yes') or the subject is not in the hospital during the whole day ('No').
Incidence of hospital readmission	Does the subject require hospital readmission after first discharge (The start date of the hospital readmission must be at least 1 day in between the end of the previous hospitalization)? Categories will be Yes (1) or No (0).

Incidence of all-cause mortality	Did the subject die after first dose of study drug? Categories will be Yes (1) or No (0).
Hospital recovery scale outcome assessed on Day 2 to 14 excluding Day 6	The hospital recovery scale outcome defined per day for Day 2 to 14 excluding Day 6 is defined analogous to the primary endpoint.
Fundamental Hospital recovery scale outcome assessed on Day 2 to 14	The fundamental hospital recovery scale reflects the status of the subject objectively independent of the opinion of the investigator (irrespective of being ready for discharge or requiring ICU level of care). The Fundamental hospital recovery scale outcome assessed on Day 2 to Day 14 is defined as follows: 6. Death – Subject died at any time on the day of assessment or earlier (all-cause mortality). 5. On invasive mechanical ventilation – Invasive mechanical ventilation is used at any time on the day of assessment. 4. In ICU 3. Non-ICU hospitalization, on supplemental oxygen – Non-ICU hospitalized on the day of assessment (including readmittance) and the subject is on supplemental oxygen. On supplemental oxygen is defined by: – Receiving supplemental oxygen through a face mask or nasal cannula. 2. Non-ICU hospitalization, without supplemental oxygen – Non-ICU hospitalized on the day of assessment (including readmittance) 1. Not hospitalized – Discharged from the hospital before the day of assessment .
Incidence of antibiotic treatment	Did the subject use antibiotic treatment after first dose of study drug? Categories will be Yes (1) or No (0). The derivation of the categories will be based on the ATC level 2 categorization of concomitant medications. Concomitant medications coded as "J01" will be indicated as antibiotic treatment.

Duration of antibiotic treatment (hours) [Duration]	The total number of hours a subject used antibiotic treatment (= event) during the period from first intake until study termination, calculated as sum of [(end date and time of event – start date and time of event)/3600], rounded to one decimal for all separate events per subject. In case the start datetime is entirely or partially unknown and the medication was used before start of first intake the date and time of first intake will be used. In case the end datetime is entirely or partially unknown and the medication was used after the trial ended, the last contact date will be used to calculate the duration. If time of the start antibiotic treatment is missing, then use 00:00. If time of the end of antibiotic treatment is missing, then use 23:59The derivation of the duration is analogous to "Total length of hospital stay".
Time to NEWS2 <= 2 (hours) [Time- to event]	The time (hours) from first study drug to first time NEWS2<=2 maintained for 24 hours i.e. the time of the first of at least 2 consecutive NEWS2 assessments with 24 hours in between. If time is missing for the NEWS2, but timepoint is available then time will be imputed: if morning then time will be 08:00, if midday then time will be 12:00, if evening then time will be 20:00. Subjects that did not maintain a NEWS2<= 2 for 24 hours until completion of the trial or withdrawal, will be censored at the time of completion of withdrawal of the study. If time is not available then it will be imputed with 23:59. If the subject died before having a NEWS2 <=2 for 24 hours, the subject will be censored at the maximum time of all subjects.
Time to clinical improvement (hours) [time- to event]	The time (hours) from first study drug to clinical improvement. Clinical improvement is defined as the minimum of the time to hospital discharge or time to NEWS2 <=2 maintained for 24 hours. Censoring will be done similarly as 'time to hospital discharge' and 'time to NEWS2<=2'.

Time to clinical failure (days) [Time-to event]	The time (in days) from first study drug intake to first clinical failure(=event). Clinical failure is defined as having one of the following events • HRS >3 The first event will be considered. In case mechanical ventilation is started multiple times, only the first start of mechanical ventilation after first study drug intake is used. Subjects without a clinical failure at the time of completion or at the time of withdrawal from the study will be censored at the date of completion or withdrawal. (Date of event or censoring–- date of first dose of study drug) + 1
Incidence of Mortality per day	Number and percentage of subjects that died and cumulative number and percentage of subjects that died per day after first study drug.

5.3.1.2. Viral kinetics

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 analysis visit. As a consequence, the series of results of a subject can be a combination of both methods (for example at baseline the NP ELISA result is used and at Day 3 the Hemagglutination Inhibition Assay result is used).

Endpoints listed below will be based on results from nasal mid-turbinate (MT) swabs taken from central testing, excluding data from leftover samples from local virology tests.

Measurement	**Formula**
Log_{10} viral load actual values	Log_{10} of the actual values as measured with qRT PCR
Viral load negativity (Log_{10} vp/mL)	Viral load will be categorized as Negative or Positive: • Negative (“TARGET NOT DETECTED”) • Positive (’TARGET DETECTED’ or an actual value).

Viral load categorization (Log10 vp/mL)	Viral load will be categorized as Target not detected, Target detected, and Quantifiable: • Target not detected • Target detected • Quantifiable
Log_{10} viral load change from baseline	Log_{10} viral load post-baseline value – log_{10} viral load baseline value
Log_{10} viral titer actual values	Log_{10} of the actual values as measured with viral culture
Viral titer negativity (Log_{10} $TCID_{50}$/mL)	Viral titer will be categorized as Negative or Positive: • Negative (lower than LOQ) • Positive (quantifiable results)
Log_{10} viral titer change from baseline	Log_{10} viral titer post-baseline value – log_{10} viral titer baseline value
Viral load $AUC_{0\text{-}10d}$ trapezoidal method	■ *Viral load AUC calculated from baseline to Day 10:* AUC is calculated by the trapezoidal summation rule, based on planned days of sampling, including the timepoints with (imputed) values available: *Sum over i of* $(t_{i+1}\text{-}t_i)*(Viral\ load_{ti+1}+Viral\ load_{ti})/2$ The following rules will be applied in the order described below to deal with missing values before calculating the Viral load AUC: • If the baseline value is missing, then the mean baseline value over all subjects in the ITT-i set will be used. • If a single or sequential intermediate value (not the baseline value) is missing, then the missing value will be replaced by linear interpolation of the two adjacent values. Note: this is done automatically when applying the trapezoidal summation rule. If Day 10 value is missing, but there is an assessment after Day 10, then this value will be used to interpolate the value of Day 10. • If the Day 10 value is missing, and there are no values available after Day 10, then it will be imputed with the last observed post-baseline value (LOCF). Note: In case no post baseline value is available the AUC will be missing.

Viral titer $AUC_{0\text{-}10d}$ trapezoidal method	Viral titer AUC calculated from baseline to Day 10: AUC is calculated by the trapezoidal summation rule, based on planned days of, including the timepoints with (imputed) values available: *Sum over i of* $(t_{i+1}-t_i)*(Viral\ titer_{ti+1}+Viral\ titer_{ti})/2$ The following rules will be applied in the order described below to deal with missing values before calculating the Viral titer AUC: • If the baseline value is missing, then the mean baseline value over all subjects in the ITT-i set will be used. • If a single or sequential intermediate value (not the baseline value) is missing, then the missing value will be replaced by linear interpolation of the two adjacent values. Note: this is done automatically when applying the trapezoidal summation rule. If Day 10 value is missing, but there is an assessment after Day 10, then this value will be used to interpolate the value of Day 10. • If the Day 10 value is missing, and there are no values available after Day 10, then it will be imputed with the last observed post-baseline value (LOCF). Note: In case no post baseline value is available the AUC will be missing.
Time to viral negativity by qRT-PCR (days) [Time-to event]	The time to viral negativity is defined as the time (in days) from first study drug intake until a subject is considered influenza A viral negative. This is the first timepoint of two consecutive timepoints with a negative nasal MT swab, i.e. the first and next assessment equal to 'negative' (ignoring missing values). In case the first 'negative' is the last available assessment the subject is considered to have reached viral negativity at this last assessment. If this doesn't occur, a subject will be censored at the time of the last observed non-negative swab + 1 day. Note that for deriving the time to viral negativity by qRT-PCR every subject is considered positive at baseline. For subjects without postbaseline records, they are censored at Day 1.
Time to viral negativity by viral culture (days) [Time-to event]	The algorithm for Time to viral negativity by viral titer is similar as 'Time to viral negativity by viral load' but viral titer assessments are used instead.

5.3.1.3. Patient Reported Outcomes

Measurement	**Formula**
Daily activities resumption	The daily activities resumption will be assessed once daily by means of the question 'Over the past 24 hours, how much has influenza interfered with your ability to carry out your daily activities?' The responses will be dichotomized: 'Not at all' and 'A little bit' will be considered as category "returned to daily activities" and responses 'Somewhat', 'Quite a Bit' and 'Very much' will be considered in category "not returned to daily activities".
Time to return to daily activities (days) [Time-to event]	The time to return to daily activities is defined as the time in days from initiation of study treatment (baseline assessment excluded) to the first of a successive series of 2 recordings in which the response is considered as returned to daily activities. The 2 successive recordings may have been done over 3 scheduled successive analysis timepoints, in case of 1 missing in between timepoint. In case the return to daily activities is not achieved, data will be censored. Censoring will be done as follows: 1) Last non-missing record in indicate return to daily activities (but insufficient recordings) Censoring will be done at the first record of return to daily activities 2) Last non-missing record does not indicate return to daily activities Censoring will be done one day (24 hours) after the last observation. The time to return to daily activities is calculated as: Date and time of event (actual) or censoring - date and time of first dose of study drug)/(3600*24), rounded to one decimal. Subjects without postbaseline records are excluded from the analysis.
Patient Global Impression of Severity of Influenza symptoms	The PGIS captures daily influenza symptom severity from the subjects' perspective per timepoint. Responses will be categorized as :"No Flu symptoms today", and "Mild", "Moderate", "Severe" or "Very Severe".

<table>
<tr><td>Patient global Impression of Change in Influenza symptoms</td><td>The PGIC[4] is aimed to capture the subject's perceptions of improvement or deterioration in the severity of influenza symptoms compared to when the subject arrived to the hospital for influenza treatment and this is done per timepoint.[5]

Categories are: "Much better", "Somewhat better", "A little better" "About the same", "A little worse", "Somewhat worse" and "Much worse".</td></tr>
<tr><td>EQ-5D dimension parameters:
Mobility,
Self-care,
Usual activities,
Pain/discomfort,
Anxiety/depression</td><td>The EQ-5D (Attachment 5)[2] descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 possible levels (no problems (level code = 1), slight problems (level code = 2), moderate problems (level code = 3), severe problems (level code = 4), extreme problems (level code = 5)) (see Table 5). Each dimension will be captured in one parameter

Table 5: EQ-5D Dimensions
<table>
<tr><th colspan="2">Dimension</th><th colspan="2">Level</th><th>Interpretation</th></tr>
<tr><td>1</td><td>Mobility</td><td>1</td><td>No problems</td><td>I have no problems in walking about</td></tr>
<tr><td></td><td></td><td>2</td><td>Slight problems</td><td>I have slight problems in walking about</td></tr>
<tr><td></td><td></td><td>3</td><td>Moderate problems</td><td>I have moderate problems in walking about</td></tr>
<tr><td></td><td></td><td>4</td><td>Severe problems</td><td>I have severe problems in walking about</td></tr>
<tr><td></td><td></td><td>5</td><td>Extreme problems</td><td>I am unable to walk about</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>2</td><td>Self-care</td><td>1</td><td>No problems</td><td>I have no problems washing or dressing myself</td></tr>
<tr><td></td><td></td><td>2</td><td>Slight problems</td><td>I have slight problems washing or dressing myself</td></tr>
<tr><td></td><td></td><td>3</td><td>Moderate problems</td><td>I have moderate problems washing or dressing myself</td></tr>
<tr><td></td><td></td><td>4</td><td>Severe problems</td><td>I have severe problems washing or dressing myself</td></tr>
<tr><td></td><td></td><td>5</td><td>Extreme problems</td><td>I am unable to wash or dress myself</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>Usual activities</td><td>1</td><td>No problems</td><td>I have no problems doing my usual activities</td></tr>
<tr><td></td><td></td><td>2</td><td>Slight problems</td><td>I have slight problems doing my usual activities</td></tr>
<tr><td></td><td></td><td>3</td><td>Moderate problems</td><td>I have moderate problems doing my usual activities</td></tr>
<tr><td></td><td></td><td>4</td><td>Severe problems</td><td>I have severe problems doing my usual activities</td></tr>
<tr><td></td><td></td><td>5</td><td>Extreme problems</td><td>I am unable to do my usual activities</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>4</td><td>Pain/discomfort</td><td>1</td><td>No problems</td><td>I have no pain or discomfort</td></tr>
<tr><td></td><td></td><td>2</td><td>Slight problems</td><td>I have slight pain or discomfort</td></tr>
<tr><td></td><td></td><td>3</td><td>Moderate problems</td><td>I have moderate pain or discomfort</td></tr>
<tr><td></td><td></td><td>4</td><td>Severe problems</td><td>I have severe pain or discomfort</td></tr>
<tr><td></td><td></td><td>5</td><td>Extreme problems</td><td>I have extreme pain or discomfort</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>5</td><td>Anxiety/depression</td><td>1</td><td>No problems</td><td>I am not anxious or depressed</td></tr>
<tr><td></td><td></td><td>2</td><td>Slight problems</td><td>I am slightly anxious or depressed</td></tr>
</table></td></tr>
</table>

	<table><tr><td></td><td></td><td>3</td><td>Moderate problems</td><td>I am moderately anxious or depressed</td></tr><tr><td></td><td></td><td>4</td><td>Severe problems</td><td>I am severely anxious or depressed</td></tr><tr><td></td><td></td><td>5</td><td>Extreme problems</td><td>I am extremely anxious or depressed</td></tr></table>
EQ-5D visual analogue scale (VAS)	EQ-5D VAS is a continuous score ranging from 0 (worst health you can imagine) to 100 (best health you can imagine).
EQ-5D VAS change from baseline	EQ-5D VAS post-baseline value – EQ-5D VAS baseline value
EQ-5D VAS clinically relevant change from baseline	The change from baseline in EQ-5D VAS will be categorized in two ways: 1. ≤-7, -6 to 6, ≥7 2. ≤-10, -9 to 9, ≥10
EQ-5D Valuation index	EQ-5D Valuation index summarizes the information of the 5 dimensions of the descriptive system. a. Assign the level code 1, 2, 3, 4 and 5 to each level of the 5 dimensions (see table) b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension. The dimensions are ordered as described in the table above. E.g. health state 12543 indicates 'no problems in walking about, slight problems washing or dressing myself, unable to do my usual activities, severe pain or discomfort, moderately anxious or depressed'. c. Assign an index value to each health state as defined in Attachment 5 where EQ-5D health state is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The algorithm is based on the valuation of EQ-5D health states using the UK TTO (=time trade-off method) based value set.
EQ-5D Valuation index change from baseline	EQ-5D valuation index post-baseline value – EQ-5D valuation index baseline value

5.3.2. Analysis Methods

Descriptive statistics

The descriptive statistics that will be shown may include the number of subjects, mean, standard deviation, standard error, 95% CI, median, range, interquartile range and geometric mean with corresponding 95% CI.

Kaplan-Meier analysis, Gehan-Wilcoxon test and Log-rank test

All Time-to event variables will be analyzed using a stratified Gehan-Wilcoxon test, a stratified log-rank test and Kaplan-Meier estimates. For endpoints where the start time is not the start of the treatment A summary table including number of subjects included in the analysis, number of subjects censored, 25th and 75th percentiles and median time-to event, with 95% confidence intervals based on log-log transformation method, and the p-values calculated based on the stratified Gehan-Wilcoxon test and stratified log-rank test will be presented.

The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment.

For all subgroup analyses, Kaplan-Meier plots will be produced per subgroup and Gehan-Wilcoxon test will be produced for each category of a subgroup.

Accelerated failure time (AFT) model

When indicated, time-to event variables will be compared between pimodivir and placebo using an accelerated failure time (AFT) model. The distribution to be used will be determined based on the goodness of fit of the model using Akaike's information criterion and will be selected from the following parametric families: lognormal, log-logistic, or Weibull. The AFT model will include the fixed, categorical effects for treatment (with placebo as the reference), the time from admission to start of treatment (for the time to hospital discharge and time to hospital discharge readiness) and stratification factors (type of baseline SOC, time of onset of symptoms and screening NEWS2). The scale parameter will be the same across groups

A summary of the final AFT model will include parameter estimates and associated standard errors, estimated accelerated failure time ratios versus placebo and associated 95% confidence intervals, and p-values. The survival curves per treatment group of the accelerated failure time model will also be shown with the Kaplan-Meier plots included in the same output.

For subgroup analyses the survival curves will be shown for each subgroup category separately.

Bootstrapping with replacement, considering also the actual proportion of subjects in each stratum, will be used to obtain a 100% sample size 10001 times. The median (95% CI) time-to event will be derived from the 10001 bootstrapped samples.

Cox Proportional Hazard model

A stratified Cox proportional hazards model will be used adjusted for the stratification factors and for the time from admission to start of treatment (for the time to hospital discharge and time to hospital discharge readiness),. The hazard ratio for the comparison of pimodivir versus placebo will be reported together with the 95% confidence interval. A Log-log plot of survival will be added to check the proportional hazard assumption of the Cox proportional hazards model.

For the subgroup analyses the Log-Log plot of survival will be shown for each subgroup category separately.

Logistic regression model

A logistic regression model (Firth's penalized likelihood approach), with treatment group and stratification factors as fixed effects, will be used to analyze binary outcomes and to obtain the odds ratios (95% CI) for the comparison of pimodivir versus placebo.

5.3.2.1. Clinical outcome

Time-to event parameters for clinical outcome

The time-to event parameters for clinical outcome will be analyzed as described above using a stratified Gehan-Wilcoxon test, a stratified log-rank test, a Kaplan‑Meier analysis, an accelerated failure time model and a Cox proportional hazards model The Gehan-Wilcoxon test is the primary analysis for time-to-event parameters. The Kaplan-Meier analysis will provide the primary estimation of time-to-event.

Duration parameters

Descriptive statistics of the duration parameters will be shown for all subjects that had the specific event. e.g. only subjects admitted to ICU will be included in the total time in ICU analysis

Total length of hospitalization, total time in ICU, total duration of antibiotics, and total time on mechanical ventilation will be analyzed by using the Hodges-Lehman approach. Corresponding 95% CIs will be presented as well.

Incidence parameters

For each parameter the number and percentage of subjects in each category and subcategory will be tabulated and listed. All Subjects in the applicable analysis set will be counted for the denominator of the proportion.

The occurrence (yes/no) as described for the incidence parameters will be analyzed using logistic regression as described above (Section 5.3.2).

The occurrence (yes/no) of influenza complications will be analyzed using logistic regression as described above for the following categories:

- the overall influenza complications
- the pulmonary complications,
- the extrapulmonary complications
- the infectious complications
- the non-infectious complications
- the major complications
- the minor complications
- the pulmonary complications including sinusitis and otitis

Hospital recovery scale outcome and fundamental hospital recovery scale outcome on Day 2 to 14

This parameter will be analyzed analogous to the primary endpoint: hospital recovery scale outcome on Day 6, but then for Day 2 to 14 with Day 6 excluded for the HRS and including Day 6 for the fundamental HRS. The proportional odds model will be applied, and the proportional odds assumption will be tested for the treatment effect. The same 5 dichotomization of the HRS will be analyzed using a logistic regression model. Also, similarly as the primary endpoint the Van Elteren test will be provided in case the proportional odds assumption is not valid. The MI analysis will not be applied.

A tabulation will be made of the (fundamental) hospital recovery scale outcomes at each day (including Day 6), taking only non-missing values into account (i.e.: the percentages of the six categories per day should sum up to 100%). A second tabulation will be made of the hospital recovery scale outcomes at each day including a category for missing values. The first day with 30% of subjects not hospitalized will be identified. All Subjects in the applicable analysis set will be counted for the denominator of the calculation.

5.3.2.2. Viral Kinetics

Viral load and viral titer over time

The actual values and change from baseline of the viral load and viral titer over time will be shown descriptively and by mean (SE) plots per analysis timepoint.

Individual AUCs from baseline to Day 10 for both viral load and viral titer will be calculated using the trapezoid method and summarized using descriptive statistics.

Viral load negativity, viral load categorization and viral titer negativity will be summarized using frequency tabulations (n and %) at each analysis visit. All subjects with lab data on the specific visits/timepoints will be used as denominator.

- *Difference in mean viral load AUC calculated from baseline to Day 10:*

Post-baseline mean viral load values up to and including Day 10 over time will be analyzed using a restricted maximum likelihood based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline viral load and baseline viral load -by-visit 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 model above will be used to estimate the difference in the viral AUCs for active versus placebo.

Post-baseline mean viral titer values up to and including Day 10 will be analyzed similarly.

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

Time to viral negativity by viral load and by viral titer
Analysis will be done analogous to the time-to event parameters for clinical outcome. The baseline viral load or viral titer will be added as covariate to the AFT and Cox Proportional Hazard model.

5.3.2.3. Patient Reported Outcomes

Time to return to daily activities
Time to return to daily activities will be analyzed analogous to the time-to event parameters for clinical outcomes.

Patient Global Impression parameters and daily activities resumption
The subject's perception of severity and changes of influenza symptoms (PGIS, PGIC) and daily activities resumption will be tabulated per parameter and per category by analysis timepoint using frequency tabulations.

EQ-5D dimension parameters
Tabulations of the number (and percentage) of subjects per parameter, response and time point will be shown per treatment group.

EQ-5D VAS, EQ-5D Valuation index
The actual values and changes from baseline will be shown descriptively and by mean (SE) plots per analysis visit.

The proportion of subjects with a clinically relevant change from baseline of 7 or more (decrease or increase) and of 10 or more (decrease or increase) will be tabulated.

Missing data

1) If – for a questionnaire – one (or more) dimensions of the descriptive system are missing then
   - The EQ-5D VAS will be included in the analysis
   - The valuation index will not be included in the analysis
   - The non-missing dimensions of EQ-5D descriptive system will be

   included in the analysis of the separate dimensions
2) If – for a questionnaire – the EQ-5D VAS is missing then
   the EQ-5D descriptive system and valuation index will be included in the analysis if complete (otherwise see 1)

6. TASTE AND SWALLOWABILITY

6.1. Definition

Taste and swallowability will only be assessed for adolescents in this study.

The acceptability of the taste will be derived from the responses to the overall question on taste, dichotomizing the responses 'None' and 'Weak' as acceptable and responses 'Moderate' or 'Strong' as unacceptable.

For swallowability, a dichotomization of the responses will be made of ‘slightly difficult’ or worse vs ‘neither difficult nor easy’ or better.

6.2. Analysis Methods

Taste and swallowability questionnaire results (collected for adolescents only who take pimodivir or placebo tablets; not applicable when tablets are administered via nasogastric tube) will be summarized per tablet intake (first and last intake of the study drug) by means of frequency tabulations of the actual responses. Additionally the number of subjects (%) will be presented by response category (including dichotomization) for swallowability and taste separately. Analyses will be done on the safety set.

7. SAFETY

All safety analyses will be done on the Safety Set.

7.1. Adverse Events

7.1.1. Definitions

Coding of AE

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Events are looked at on the level of their preferred term.

Treatment-emergent AE

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 and up to and including the end of the follow-up phase.

An AE, at the preferred term level, is considered treatment-emergent if:

- an AE starts after or at first dose of study drug and
    - The AE was not present prior to first dose of study drug
- an AE was present prior to first dose of study drug:
    - the same AE (based on preferred term) starts at the end date or the day after the end date of the AE present prior to first dose and new AE has worsened, ie an increase in toxicity grade or changed to an SAE
    - the same AE (based on preferred term) started 2 or more days after the end date of the AE present prior to first dose
- The start date of the AE is missing
- The start time of the AE is missing, and the AE was not present the day before first dose of study drug, and the start date of the AE is the same as the start date of first dose of study drug
- The day is missing of the AE start date but month and year are the same as month and year of first study drug intake.
- The month is missing of the AE start date but the year is the same as the year of the first study drug intake.

Phase allocation of AE

Adverse events present in the SDTM database are allocated to phases based on their start date and time. If the start date and time of an event falls between (or on) the start and stop date and time of a phase, the AE is attributed to that phase (treatment-emergent principle).

Rule: phase start datetime ≤ AE start datetime ≤ phase stop datetime.

Incomplete AE dates and or times (i.e. time and/or day and/or month and/or year missing):

- In case of partial AE start dates and or times, the events are allocated to the phases using the available partial information on start and end datetime; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to

the month and year information of the phases. This rule may lead to multiplication of the event as a consequence of its assignment to multiple phases or subperiods.

- In case of a completely missing AE start date, the event is allocated to the first active treatment phase and subperiod, except if the end date of the AE falls before the start of this active treatment phase and subperiod.
- In case of a completely missing AE end date, the following rules apply:
  - in case the date is identified as unknown the date will remain missing;
  - in case the date is not flagged as unknown the date is assumed to be the cut-off date of the analysis for subjects still ongoing in the study, and the end date of the last phase for subjects who discontinued or completed the study.

Examples:

Screening phase: start date: 02JAN2017 - stop date: 28JAN2017
Treatment phase: start date: 29JAN2017 - stop date: 12AUG2017

1) Adverse event: start date: JAN2017- stop date: 15JUL2017
   As the AE start date only has information about month and year, only this information will be used from the phases and therefore the AE will be assigned to the screening phase as well as to the treatment phase.
2) Adverse event: start date: JAN2017- stop date 27JAN2017 As the AE stops before or at the start of the treatment phase, it is only assigned to the Screening phase.

Remarks: In addition to the date information, time information is taken into account to allocate AEs to phases.

Adverse events

The variables attributed to adverse events are

- AE term (verbatim and MedDRA preferred term and system organ class)
- Onset datetime, End datetime and duration of AE
- Serious AE (Yes/No), if yes classification will be listed
- Toxicity grade (Mild, Moderate, Severe, Potentially life-threatening)
- Action taken with study treatment (Dose not changed, Dose interrupted, Drug withdrawn, Not applicable, Unknown)
- Relation to study treatment (Not related, Doubtful, Possible, Probable, Very likely)
- Outcome of AE
- AE leading to death (Yes/No)
- Concomitant treatment taken for AE (Yes/No)
- Influenza-related complication (Yes/No)
- Required hospitalization/prolonged hospitalization (Yes/No)

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 Attachment 1: for the classification of AEs into Anticipated Events and Anticipated Event Groups):

- 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)

Influenza-related complications

The categories of influenza-related complications are defined in 5.3.1.1

Confirmed diarrhea events

Additional details required to confirm a diarrhea event, including number of loose stools episodes per day and stool consistency, will be collected for subjects who report a diarrhea type event.

A confirmed diarrhea event is defined as three or more loose stools episodes per day with a consistency of 'loose' or 'watery'.

7.1.2. Analysis Methods

Treatment-emergent adverse events

There will be no formal statistical testing unless indicated otherwise.

A summary will be provided for the following TEAEs per phase (Treatment phase, Follow-up phase), subperiod and for the combination of Treatment and Follow-up phase:

- any adverse events,
- serious adverse events,
- deaths due to AE,
- adverse events by worst toxicity grade,
- AEs of worst grade 3 or 4
- AEs of worst grade 3
- AEs of worst grade 4
- AEs at least possibly related to study drug,
- AEs for which study drug was temporarily stopped,
- AEs for which study drug was permanently stopped,
- AEs leading to study discontinuation
- serious adverse events that were at least possibly related to study drug,
- Adjudicated influenza related complications
- COVID-19 AEs
- COVID-19 Serious AEs
- COVID-19 Non-serious AEs

The adverse events will be shown by MedDRA system organ class and preferred term, in order of descending overall frequency in the pimodivir group. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and per phase (Treatment phase, Follow-up phase), subperiod and for the combination of Treatment and Follow-up phase. The tabulations will be provided for the following categories:

- any adverse events
- serious adverse events
- AEs at least possibly related to study drug
- AEs for which study drug was temporarily stopped
- AEs for which study drug was permanently stopped
- AEs leading to study discontinuation
- serious adverse events that were at least possibly related to study drug
- AEs related to COVID-19 infection
- Serious AEs related COVID-19 infection
- AEs related to COVID-19 infection leading to death

and in addition for treatment emergent adverse events with incidence of at least 5% in any treatment group.

In order to fulfil requirements for the plain language summary document and presentations for EudraCT the following adverse event categories will be shown by MedDRA system organ class and preferred term per phase (Treatment phase, Follow-up phase) and subperiods (treatment subperiod and treatment extension subperiod) and for the combination of Treatment and Follow-up phases. No tabulations by subgroups will be provided for these categories:

- deaths due to AEs that were at least possibly related to study drug
- AEs for which study drug was permanently stopped that were at least possibly related to study drug
- non-serious AEs that were at least possibly related to study drug
- any non-serious AEs

AEs leading to death, SAEs, AEs leading to dose interruption or permanent stop of study drug, AEs related to COVID-19 infection will be listed separately. All AEs will be listed in an individual subject data listing, including pre-treatment AEs. All listings will be provided for the safety set.

The duration (in days) of an AE is calculated based on the AE start date and AE end date as:

AE duration = AE end date – AE start date +1

Note that the AE duration will be calculated in case the start date and end date is fully known, in case of partial or missing start and end dates the AE duration will be put on missing.

Anticipated Events

Frequency tabulations of anticipated events and anticipated event grouped terms will be shown for treatment phase and subperiods, follow-up phase and for the combination of treatment + follow-up phases. The tabulation will show per treatment the number (%) of subjects with serious, non-serious and total anticipated events and anticipated event grouped terms and a one-sided p-value of Fisher exact test for anticipated events and anticipated event grouped terms.

A listing of the anticipated events will be added.

More details on the anticipated events analysis can be found in the Anticipated Events Safety Monitoring plan.

Influenza-related complications

Adverse Events adjudicated as influenza-related complications will be will be tabulated for treatment phase and subperiods, follow-up phase and for the combination of treatment + follow-up phases.

Adverse events that were assessed by the investigator as influenza-related complications will also be tabulated by category, subcategory (see Section 5.3.1.1) and adverse event, for treatment phase and subperiods, follow-up phase and for the combination of treatment and follow-up phases. A listing showing the AEs reported as influenza-related complications and complication information will be made linking the information to the AE listing. Additional analyses on adjudicated influenza-related complications are described in Section 5.3.2.1.

Confirmed diarrhea events

The number and percentage of subjects who experience at least 1 occurrence of confirmed diarrhea events will be summarized by treatment group and per phase (Treatment phase, Follow-up phase) and subperiods (treatment subperiod and treatment extension subperiod) and for the combination of Treatment and Follow-up phases.

For all subjects that complete the additional diarrhea form, a cross-tabulation of number of loose stools episodes per day (categorized as 1, 2, 3 or more) versus stool consistency will be produced by treatment group and per phase (Treatment phase, Follow-up phase) and for the combination of Treatment and Follow-up phases. If a subject has more than 1 diarrhea event per phase, then the worst response from all events in that phase will be tabulated.

Descriptive statistics will be produced by treatment group for the number of days from first dose of study drug to onset of first diarrhea event and for total duration of diarrhea events. A frequency tabulation will be produced by treatment group for the number of days from last dose of study drug to resolution of last diarrhea event.

Frequency tabulations will be produced by treatment group and per phase (Treatment phase, Follow-up phase and subperiods) and for the combination of Treatment and Follow-up phases for the severity grade of the diarrhea event and for whether any concomitant medication was used to treat the diarrhea event.

No tabulations by subgroups will be provided.

All information recorded on the specific diarrhea form will be listed.

7.2. Clinical Laboratory Tests

7.2.1. Definitions

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.

Imputations of numerical values expressed as characters

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 the cut-off value decreased or increased with one unit respectively
- '≤x' or '≥x': imputation by x.

Toxicity grades and abnormalities for laboratory parameters:

The laboratory abnormalities will be determined according to the criteria specified in the WHO grading table[12] (see Attachment 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 for each subject the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period, per phase (treatment, follow-up and combination treatment + follow-up) and per subperiod (treatment, treatment extension) separately, including all post-baseline 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-baseline, both abnormalities are shown in the tables. (This implies 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.

Treatment-emergent definition for toxicity grades and abnormalities

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" post-baseline (or vice versa) is also treatment-emergent.

7.2.2. Analysis Methods

Actual values and changes from baseline will be summarized by treatment group at each scheduled timepoint.

A tabulation of the toxicities/abnormalities per timepoint will be presented. This table will also show the number and percentage of subjects per toxicity/abnormality, the number and percentage of subjects per treatment-emergent abnormality, and the cumulative number of subjects per treatment-emergent abnormality per post-baseline timepoint. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

Additionally, a tabulation of the worst toxicity/abnormality will be presented. This table will show the number and percentage of subjects per worst toxicity/abnormality. A cross-tabulation of the worst toxicity/abnormality versus baseline will be presented per phase (treatment, follow-up and combination treatment + follow-up) and per subperiod (treatment, treatment extension). 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.

For tabulations of hyperglycemia, the results will also be presented for the subgroup of subjects that had been fasting for at least 10 hours.

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

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

Grade 3 or higher toxicity laboratory values will be listed separately

Frequency tables (n %) will be produced for the categorical urinalysis parameters by treatment group at each scheduled timepoint. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

All urinalysis results will be listed.

7.3. Vital signs

7.3.1. Definitions

Vital signs (including temperature, pulse rate, respiratory rate, and blood pressure), peripheral capillary oxygen saturation, and level of consciousness (AVPU) will be included in the analysis.

Vital Signs abnormalities will be determined according to the WHO grading scale boundaries defined in Attachment 3, Table 4: Resolution Criteria for Vital Signs.

Worst abnormalities are determined over the whole observational period and per phase (treatment, follow-up and combination treatment + follow-up) and per subperiod (treatment, treatment extension), including all post-baseline scheduled and unscheduled measurements.

An abnormality (based on normal ranges) will be considered treatment-emergent if it is worse than the baseline abnormality. If the baseline abnormality is missing, the abnormality is always considered as treatment-emergent. A shift from "abnormally low" at baseline to "abnormally high" post-baseline (or vice versa) is also treatment-emergent.

Assessments (except oxygen saturation) taken while the subject was not in a supine position will not be included in descriptive statistics but will be considered in determining worst case values.

7.3.2. Analysis Methods

Actual values and changes from baseline will be summarized by treatment group at each scheduled timepoint.

A tabulation of the abnormalities per timepoint will be presented. This table will also show the number and percentage of subjects per abnormality, the number and percentage of subjects per treatment-emergent abnormality, and the cumulative number of subjects per treatment-emergent abnormality per post-baseline timepoint. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

Additionally, a tabulation of the worst abnormality will be presented. This table will show the number and percentage of subjects per worst abnormality.

A cross-tabulation of the worst abnormality versus baseline will be presented per phase (treatment, follow-up and combination treatment + follow-up) and per subperiod (treatment, treatment extension). This table will also show the number and percentage of subjects per worst abnormality, the number and percentage of subjects per treatment-emergent worst abnormality, and the cumulative number of subjects per treatment-emergent abnormality.

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

Vital signs data for subjects having at least one treatment-emergent abnormality will be listed.

7.4. Physical examinations

Abnormal physical examination results will be listed.

7.5. Electrocardiogram

PR interval, QT interval, QRS interval, Heart Rate and QTc intervals using Bazett's correction formula and Fridericia's correction formula will be investigated[1]. QTc values will be used as reported, they will not be recalculated. If the ECG is performed in triplicates the mean of the non-missing ECG recordings will be used as the value for each specific parameter and timepoint.

7.5.1. Definitions

ECG abnormalities will be determined according to the boundaries defined in Attachment 4.

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

Assessments taken while the subject was not in a supine position will not be included in descriptive statistics but will be considered in determining worst case values.

7.5.2. Analysis Methods

Actual values and changes from baseline will be summarized by treatment group at each scheduled timepoint.

A tabulation of the abnormalities per timepoint will be presented. This table will also show the number and percentage of subjects per abnormality, the number and percentage of subjects per treatment-emergent abnormality, and the cumulative number of subjects per treatment-emergent abnormality per post-baseline timepoint. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

A cross-tabulation of the worst abnormalities versus baseline will be presented per phase (treatment and follow-up, treatment and follow-up phase and subperiods). This table will also show the number and percentage of subjects per worst abnormality, the number and percentage of subjects per treatment-emergent abnormality, and the cumulative number of subjects per treatment-emergent abnormality.

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

A frequency tabulation of the QT/QTc change categories at Day 28 versus baseline will be presented.

ECG data for subjects having at least one treatment-emergent abnormality will be listed.

7.6. National Early Warning Score

7.6.1. Definitions

NEWS

The NEW Score[7] is an aggregated score with a range from 0 to 20 calculated as the sum of the scores per parameter (see Table 6, all parameters are based on the VS dataset and CM). However, in case information for a parameter is missing the NEW score cannot be calculated.

Table 6: 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

Note: The following parameters for the NEWS for subjects that are on invasive mechanically ventilation while NEWS is assessed will be adjusted:

Oxygen saturation = 90%
Any Supplemental oxygen = YES
Level of Consciousness =Unresponsive

The observed data values for these parameters will be ignored and replaced by above values. Subsequently all parameters will be evaluated according to Table 6.

NEWS2

The original NEWS was designed for patients whose normal range for oxygen saturation is between 96 – 100%. For SpO2 values below this, the NEW score increases. The NEWS is updated by a new version, NEWS2[8], to more accurately score the acute-illness severity of subjects with routinely low oxygen saturation. Subjects that have a prescribed oxygen saturation requirement of

88 - 92%, i.e. patients with hypercapnic respiratory failure, often referred to as 'type 2' respiratory failure (Although COPD is the most common cause of hypercapnic respiratory failure, there are other causes such as morbid obesity, chest-wall deformities or neuromuscular disorders) will be evaluated with the new SpO2 scoring scale 2.

In addition, a new consciousness level is added to capture a change in confusion: new Confusion (C). Note: The following parameters for the NEWS2 for subjects that are on invasive mechanical ventilation and that met the criteria for the SpO2 scale 2 will be adjusted:

Oxygen saturation = 82%
Any Supplemental oxygen = YES
Level of Consciousness =Unresponsive

The observed data values for these parameters will be ignored and replaced by above values. Subsequently all parameters will be evaluated according to Table 7

Table 7: The NEWS2 scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Note: the physiological parameter: 'Air or Oxygen' is evaluated by checking the use of the supplemental oxygen. For the SpO2 scale 2, to evaluate if the assessment is taken on room air or on oxygen, the answer to the question 'Was this measurement taken on room air' is used. Oxygen saturation measurements lower or equal to 92% are scored 0 to 3 in the SpO2 scale 2 independent if the measurement was taken on room air or not. Oxygen saturation measurements of 92% or more on room air will have a score 0 for the SpO2 scale 2. Oxygen saturation measurements of 93 or more taken on oxygen are scored 1 to 3 in the SpO2 scale 2 (last 3 columns)

The subjects for who the oxygen saturations levels need to be evaluated with the SpO_2 scale 2, met following criteria at (or before) the time of randomization:

- Oxygen saturation of the last assessment before randomizing is lower or equal to 92%
- Chronic oxygen was used

The SpO_2 scale 2 will then be used for the NEWS2 calculation throughout the rest of the trial for the subject. The SpO_2 scale 1 will be used for the other subjects.

Note that for the NEWS2 by timepoint a subject receives supplemental oxygen if he received oxygen at the time of the measurement of oxygen saturation. For the NEWS(2) stratification this is checked within the randomization window as explained in Section 5.1.4

NEWS2 Category
The NEWS 2 will be categorized into its clinical risk according to the following categories:

- No clinical risk: (score 0)
- 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)

In case a parameter is missing to calculate the NEWS 2 but based on the available information the NEWS 2 is 7 or more, the NEWS2 category will be 'High clinical risk'.

7.6.2. Analysis Methods

Descriptive statistics of the NEWS2 and the change from baseline will be shown by analysis timepoint. Additionally, a mean +/- SE graph of the scores over time will be provided.

A frequency table of the ACVPU score by timepoint and treatment group will be provided. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

A tabulation of the clinical risk categories will be made per analysis timepoint. Include in this table the safety follow-up visit, the Day 28 final study visit and the last study visit.

A listing of the NEWS2 by analysis timepoint for each subject will be provided.

8. RESISTANCE

8.1. Viral Phenotype

The pimodivir EC_{50} and oseltamivir IC_{50} with their fold change values will be analyzed at baseline and at all post-baseline visits with available data (FC = fold change in EC_{50} (IC_{50}) value).

FC is calculated as the EC50 (or IC50) of the subject's influenza strain divided by the EC50 (or IC50) of a reference strain. If the patient EC50 (or IC50) is censored, the fold change value gets the same censor, e.g. patient EC50 = >20 nM, reference EC50 = 4nM, Fold Change value >5.

The following output will be provided:

- Emerging phenotypic resistance: descriptive statistics for FC in EC_{50} and IC_{50} value for pimodivir and oseltamivir respectively at baseline and at all post-baseline visits with available data. The number (%) of subjects by treatment arm with censored phenotype data (by lower and upper bound) at baseline and at all post-baseline visits with available data will also be shown.
- Descriptive statistics for fold change ratio of all post-baseline visits with available data 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 timepoints including screening/baseline.

8.2. Viral Genotype

Assessment of viral sequences will be done to determine amino-acid substitutions that may be associated with resistance to pimodivir and to other influenza antivirals if present as part of the SOC. To that end, genotypic data for PB2, PB1, PA, NA, HA and optionally other genome segments of the influenza virus will be gathered.

All positions in the gathered regions will be analyzed for all samples, overall and by influenza subtype.

The gathered regions most relevant for pimodivir are PB2, PB1 and PA, those for neuraminidase inhibitors (NAI) (including oseltamivir) are NA and HA

The following 12 amino-acid positions in PB2 are of interest: 306, 323, 324, 325, 337, 357, 363, 376, 378, 404, 406, 431, and 510.

The following mutations in NA, associated with resistance to oseltamivir, 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 timepoint.

The baseline is the collection of all polymorphisms present at any timepoint up to the first intake of study. A table with an overview of the time points underlying the "baseline" will be generated.

Data will be summarized using frequency tabulations (n and %). Displays and individual mutations should be presented for each genome segment separately (i.e. PB1, PB2, PA, NA and HA 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 timepoints including screening/baseline including viral load data (include influenza subtype and influenza subtype category). A patient profile will be created including this data supplemented with the phenotypic data.

9. PHARMACOKINETICS/PHARMACODYNAMICS

Blood samples for PK assessments of pimodivir will be collected at the Day 1, 3, 5, 6 and/or Day 7 visit depending on when the subject is discharged from the hospital.

Descriptive statistics of pimodivir plasma concentration over time will be tabulated for the PK analysis set.

9.1. Pharmacokinetics

Based on the individual plasma concentration-time data from all subjects, exposure parameters of pimodivir will be derived using population PK modelling. The following exposure parameters will be derived for the samples collected after the first intake (Day 1), after the 5th intake (Day 3) and after the last intake (the last intake can be on Day 5, 6 or 7 and will be reported as Day 5 in the tables): AUC_{12h}, C_{trough}, and, if feasible, C_{max}, and T_{max}.

Descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum, maximum, and interquartile range will be calculated at available timepoints for all available parameters for the PK analysis set.

9.2. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/Pharmacodynamic relationships will be analyzed for the PD analysis set. The exposure parameters AUC_{12h} and C_{trough} will be categorized into quartiles for Day 1, Day 3 and Day 5 (i.e.: after the last intake, this can be on Day 5, Day 6 or Day 7) (if available). Relationships of these parameters with the primary and selected secondary efficacy endpoints will be explored as follows.

The distribution of subjects over the hospital recovery scale on Day 6 will be tabulated per quartile for each exposure parameter for each PK timepoint.

The number and percentage of subjects with treatment-emergent adjudicated influenza complications will be tabulated for each quartile for each exposure parameter for each PK timepoint.

The Kaplan Meier estimates for the time to hospital discharge will be produced per quartile for each exposure parameter for each PK timepoint.

The Kaplan Meier estimates for the time from ICU admission to ICU discharge will be produced per each quartile for each exposure parameter for each PK timepoint.

The Kaplan Meier estimates for the time to return to daily activities will be produced per quartile for each exposure parameter for each PK timepoint.

The Kaplan Meier estimates for the time from start of mechanical ventilation to end of mechanical ventilation will be produced per each quartile for each exposure parameter for each PK timepoint.

The number and percentage of subjects readmitted to the hospital after the first discharge will be tabulated for each quartile for each exposure parameter for each PK timepoint.

Relationships of AUC_{12h} with safety will be explored as follows. The number and percentage of subjects with the following treatment-emergent adverse events by AUC_{12h} quartile for each PK timepoint will be tabulated:

- Any AE
- AEs of worst grade 3 or 4
- Deaths due to AE
- Serious AEs
- AEs for which study drug was permanently stopped
- AEs at least possibly related to study drug
- Confirmed diarrhea events

A frequency table of the worst treatment-emergent toxicity grades versus AUC_{12h} quartile will be presented for the laboratory parameters AST, ALT, and total bilirubin.

Separate frequency table will be produced for the worst treatment-emergent toxicity grades at each PK timepoint.

10. HEALTH ECONOMICS

Following medical resource utilization data will be explored

10.1. Definitions

Measurement	**Formula**
Number of medical care encounters	Medical care encounters other than those mandated per trial protocol, including surgeries and other selected procedures (inpatient and outpatient), as recorded on the eCRF. The number of medical care encounters is derived as the frequency of the medical encounters other than those mandated in the protocol (eCRF).
Type of practitioner for hospital outpatient department encounters	Type of practitioner as recorded in the eCRF in case of Outpatient Department is selected.
Frequency of visits of outpatient medical care encounters	Frequency of visits will be provided per outpatient medical encounter type (Hospital Outpatient Department Laboratory Department, Medical Practitioner Office, Home Care)
Number of outpatient medical care encounters	Similar to the description for number of medical care encounters, but only for outpatient medical care encounters, as recorded on the eCRF (Hospital Outpatient Department, Laboratory Department, Medical Practitioner Office, Home Care).

10.2. Analysis Methods

Frequency tabulations of medical care encounters, per category (as defined above) and by medical encounter type, will be provided.

Frequency tabulations of the frequency of visits will be provided, per following medical encounter types:

- Hospital Outpatient Department,
- Laboratory Department,
- Medical Practitioner Office,
- Home Care

Frequency tabulations of the type of practitioner will be provided, for the Hospital Outpatient Department.

REFERENCES

1. Guideline, I. H. T. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. Recommended for adoption at Step; 2006; 4.
2. Herdman M., Gudex C., Lloyd A., Janssen M. F., Kind P., Parkin D., Bonsel G., Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011; 20:1727-36
3. Hodges J.L., Lehmann E.L., Estimates of location based on rank tests. The Annals of Mathematical Statistics. 1963; 34:598-611
4. Hurst H., Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J. Manipulative Physiol Ther. 2004;27:26-35.
5. Jaeschke R., Singer J., Guyatt G.H.. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-415.
6. Lehmann E. L. Nonparametric confidence intervals for a shift parameter. The Annals of Mathematical Statistics 1963; 34:1507–1512.
7. Royal College of Physicians of London. National early warning score (NEWS): standardising the assessment of acute-illness severity in the NHS; 2012. www.rcplondon.ac.uk/resources/national-earlywarning-score-news
8. Royal College of Physicians of London. National early warning score (NEWS) 2: standardising the assessment of acute-illness severity in the NHS; 2017. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2
9. United Nations publication, Standard Country or Area Codes for Statistical Use (M49 standard), https://unstats.un.org/unsd/methodology/m49/
10. 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.
11. Whitehead J. Sample size calculations for ordered categorical data, 1993. Statistics in medicine; 12:2257-2271.
12. World Health Organization. "WHO toxicity grading scale for determining the severity of adverse events."; 2003

ATTACHMENTS

ATTACHMENT 1. : ANTICIPATED EVENTS AND ANTICIPATED EVENT GROUPS

Table 8 shows an overview of the anticipated event groups with group number.
Table 9 indicates which adverse event preferred terms (MedDRA PT) are Anticipated Events (AnE) and Closely Related Medical Events (ME) based on MedDRA Version 18.1. These adverse events will be classified as an Anticipated Event according to the protocol term and are grouped into Anticipated Event Groups.

Table 8: Anticipated Event groups

Group Number	*Grouped Term*
Group 1	Infections and infestations
Group 2	Diabetic complications

Table 9: Anticipated Events (AnE) and Closely Related Medical Events (ME).

Protocol Term	*AnE*	*ME*	*MedDRA PT **	*MedDRA Code**	*Grouped Term*	*Group Number*
Pneumonia	☒	☐	Pneumonia	10035664	Infections and infestations	1
Pneumonia	☐	☒	Enterobacter pneumonia	10054218	Infections and infestations	1
Pneumonia	☐	☒	Pneumonia haemophilus	10035702	Infections and infestations	1
Pneumonia	☐	☒	Pneumonia staphylococcal	10035734	Infections and infestations	1
Pneumonia	☐	☒	Pneumonia streptococcal	10035735	Infections and infestations	1
Bronchitis	☒	☐	Bronchitis	10006451	Infections and infestations	1
Bronchitis	☐	☒	Bronchitis bacterial	10061736	Infections and infestations	1
Bronchitis	☐	☒	Bronchitis haemophilus	10006460	Infections and infestations	1
Sinus infection	☒	☐	Sinusitis[1]	10040753	Infections and infestations	1
Sinus infection	☐	☒	Acute sinusitis[1]	10001076	Infections and infestations	1

Protocol Term	*AnE*	*ME*	*MedDRA PT **	*MedDRA Code**	*Grouped Term*	*Group Number*
Sinus infection	☐	☒	Chronic sinusitis[1]	10009137	Infections and infestations	1
Sinus infection	☐	☒	Viral sinusitis	10051513	Infections and infestations	1
Ear infection	☒	☐	Ear infection	10014011	Infections and infestations	1
Ear infection	☐	☒	Middle ear effusion	10062545	Infections and infestations	1
Ear infection	☐	☒	Otitis externa	10033072	Infections and infestations	1
Ear infection	☐	☒	Otitis media	10033078	Infections and infestations	1
Ear infection	☐	☒	Otitis media acute	10033079	Infections and infestations	1
Worsening of asthma, asthma attack[2]	☐	☒	Asthma	10003553	NA	
Worsening of asthma, asthma attack[2]	☐	☒	Asthmatic crisis	10064823	NA	
Worsening of asthma, asthma attack[2]	☐	☒	Status asthmaticus	10041961	NA	
COPD exacerbation [3]	☒	☐	Chronic obstructive pulmonary disease	10009033	NA	
COPD exacerbation [3]	☐	☒	Emphysema	10014561	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Sickle cell anaemia	10040641	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Sickle cell anaemia with crisis	10040642	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Acute chest syndrome	10051895	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Ischaemic stroke	10061256	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Embolic stroke	10014498	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Deep vein thrombosis	10051055	NA	
Complications of sickle cell disease, sickle cell crisis[4]	☐	☒	Pulmonary embolism	10037377	NA	
Complications of diabetes mellitus, diabetic ketoacidosis[4]	☒	☐	Diabetic complication	10061104	Diabetic complications	2

Protocol Term	*AnE*	*ME*	*MedDRA PT **	*MedDRA Code**	*Grouped Term*	*Group Number*
Complications of diabetes mellitus, diabetic ketoacidosis[4]	☒	☐	Diabetic ketoacidosis	10012671	Diabetic complications	2
Complications of diabetes mellitus, diabetic ketoacidosis[4]	☐	☒	Diabetes mellitus[5]	10012601	Diabetic complications	2
Complications of diabetes mellitus, diabetic ketoacidosis[4]	☐	☒	Diabetic ketoacidotic hyperglycaemic coma	10012672	Diabetic complications	2
Complications of diabetes mellitus, diabetic ketoacidosis[4]	☐	☒	Hypoglycaemia	10020993	Diabetic complications	2
Complications of diabetes mellitus diabetic ketoacidosis[4]	☐	☒	Diabetic metabolic decompensation	100126655	Diabetic complications	2
Acute Respiartory Distress Syndrome (ARDS)	☒	☐	Acute respiratory distress syndrome	10001052	NA	
Acute Respiartory Distress Syndrome (ARDS)	☐	☒	Acute respiratory failure[6]	10001053	NA	

[1] Infectious etiology only

[2] 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.

[3] 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.

[4] 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.

[5] Please note that diabetes mellitus aggravated and diabetes mellitus exacerbated codes to a PT of diabetes mellitus.

[6] This event will be considered anticipated only if it occurs in the context of ARDS

ATTACHMENT 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

Item	Grade 1	Grade 2	Grade 3	Grade 4
Chemistries				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement Rx required or hospitalization required	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany
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

Item	Grade 1	Grade 2	Grade 3	Grade 4
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
CPK*	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 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
Lipase*	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
* Grading based on Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.0, November 2014.				
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

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused
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

Item	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
Neuro & Neuromuscular				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and Rx required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; Rx required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Other Parameters				

Item	Grade 1	Grade 2	Grade 3	Grade 4
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

ATTACHMENT 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

	Vital Signs parameter		
Abnormality Code	Temperature (°C/°F)	Respiratory rate (breaths per minute)	Oxygen Saturation (%)
Normal			≥95% - 100%
Grade 1 or mild	37.7 - 38.5 °C or 100.0 - 101.5 °F	17-20	≥90% - <95%
Grade 2 or moderate	38.6 - 39.5 °C or 101.6 - 102.9 °F	21-25	≥85% - <90%
Grade 3 or severe	39.6 - 40.5 °C or 103.0 - 105.0 °F	>25	<85%
Grade 4 or potentially life-threatening	>40.5°C or >105.0°F		

ATTACHMENT 4. : ECG ABNORMALITIES

The following abnormalities are defined for ECG:

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

ATTACHMENT 5. : EQ-5D VALUATION INDEX

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
11111	1	11242	0,498	11423	0,606	11554	0,018
11112	0,879	11243	0,484	11424	0,437	11555	-0,066
11113	0,848	11244	0,323	11425	0,26	12111	0,846
11114	0,635	11245	0,157	11431	0,653	12112	0,779
11115	0,414	11251	0,235	11432	0,596	12113	0,761
11121	0,837	11252	0,179	11433	0,582	12114	0,548
11122	0,768	11253	0,164	11434	0,412	12115	0,327
11123	0,75	11254	0,083	11435	0,236	12121	0,737
11124	0,537	11255	-0,001	11441	0,475	12122	0,678
11125	0,316	11311	0,883	11442	0,419	12123	0,663
11131	0,796	11312	0,827	11443	0,404	12124	0,45
11132	0,74	11313	0,812	11444	0,27	12125	0,229
11133	0,725	11314	0,599	11445	0,131	12131	0,709
11134	0,512	11315	0,378	11451	0,209	12132	0,653
11135	0,291	11321	0,785	11452	0,153	12133	0,638
11141	0,584	11322	0,728	11453	0,138	12134	0,425
11142	0,527	11323	0,714	11454	0,057	12135	0,204
11143	0,513	11324	0,501	11455	-0,027	12141	0,497
11144	0,352	11325	0,28	11511	0,556	12142	0,441
11145	0,186	11331	0,76	11512	0,5	12143	0,426
11151	0,264	11332	0,704	11513	0,485	12144	0,266
11152	0,208	11333	0,689	11514	0,404	12145	0,099
11153	0,193	11334	0,476	11515	0,32	12151	0,177
11154	0,112	11335	0,255	11521	0,458	12152	0,121
11155	0,028	11341	0,548	11522	0,401	12153	0,106
11211	0,906	11342	0,491	11523	0,387	12154	0,025
11212	0,837	11343	0,477	11524	0,306	12155	-0,059
11213	0,819	11344	0,316	11525	0,222	12211	0,806
11214	0,606	11345	0,15	11531	0,433	12212	0,748
11215	0,385	11351	0,228	11532	0,377	12213	0,733
11221	0,795	11352	0,172	11533	0,362	12214	0,52
11222	0,736	11353	0,157	11534	0,281	12215	0,299
11223	0,721	11354	0,076	11535	0,197	12221	0,706
11224	0,508	11355	-0,008	11541	0,328	12222	0,649
11225	0,287	11411	0,776	11542	0,272	12223	0,634
11231	0,767	11412	0,719	11543	0,257	12224	0,421
11232	0,711	11413	0,705	11544	0,176	12225	0,2
11233	0,696	11414	0,535	11545	0,092	12231	0,681
11234	0,483	11415	0,359	11551	0,17	12232	0,624
11235	0,262	11421	0,677	11552	0,114	12233	0,61
11241	0,555	11422	0,621	11553	0,099	12234	0,397

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
12235	0,176	12424	0,35	13113	0,744	13252	0,075
12241	0,468	12425	0,174	13114	0,531	13253	0,06
12242	0,412	12431	0,566	13115	0,31	13254	-0,021
12243	0,397	12432	0,51	13121	0,717	13255	-0,105
12244	0,237	12433	0,495	13122	0,66	13311	0,779
12245	0,071	12434	0,325	13123	0,646	13312	0,723
12251	0,149	12435	0,149	13124	0,433	13313	0,708
12252	0,092	12441	0,389	13125	0,212	13314	0,495
12253	0,078	12442	0,332	13131	0,692	13315	0,274
12254	-0,003	12443	0,318	13132	0,636	13321	0,681
12255	-0,088	12444	0,184	13133	0,621	13322	0,624
12311	0,796	12445	0,044	13134	0,408	13323	0,61
12312	0,74	12451	0,122	13135	0,187	13324	0,397
12313	0,725	12452	0,066	13141	0,48	13325	0,176
12314	0,512	12453	0,051	13142	0,423	13331	0,656
12315	0,291	12454	-0,03	13143	0,409	13332	0,6
12321	0,698	12455	-0,114	13144	0,248	13333	0,585
12322	0,642	12511	0,469	13145	0,082	13334	0,372
12323	0,627	12512	0,413	13151	0,16	13335	0,151
12324	0,414	12513	0,398	13152	0,104	13341	0,444
12325	0,193	12514	0,317	13153	0,089	13342	0,387
12331	0,673	12515	0,233	13154	0,008	13343	0,373
12332	0,617	12521	0,371	13155	-0,076	13344	0,212
12333	0,602	12522	0,315	13211	0,786	13345	0,046
12334	0,389	12523	0,3	13212	0,73	13351	0,124
12335	0,168	12524	0,219	13213	0,715	13352	0,068
12341	0,461	12525	0,135	13214	0,502	13353	0,053
12342	0,405	12531	0,346	13215	0,281	13354	-0,028
12343	0,39	12532	0,29	13221	0,688	13355	-0,112
12344	0,23	12533	0,275	13222	0,631	13411	0,672
12345	0,063	12534	0,194	13223	0,617	13412	0,615
12351	0,141	12535	0,11	13224	0,404	13413	0,601
12352	0,085	12541	0,241	13225	0,183	13414	0,431
12353	0,07	12542	0,185	13231	0,663	13415	0,255
12354	-0,011	12543	0,17	13232	0,607	13421	0,573
12355	-0,095	12544	0,089	13233	0,592	13422	0,517
12411	0,689	12545	0,005	13234	0,379	13423	0,502
12412	0,633	12551	0,083	13235	0,158	13424	0,333
12413	0,618	12552	0,027	13241	0,451	13425	0,156
12414	0,448	12553	0,012	13242	0,394	13431	0,549
12415	0,272	12554	-0,069	13243	0,38	13432	0,492
12421	0,591	12555	-0,153	13244	0,219	13433	0,478
12422	0,534	13111	0,815	13245	0,053	13434	0,308
12423	0,52	13112	0,759	13251	0,131	13435	0,132

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
13441	0,371	14125	0,185	14314	0,435	14453	0,007
13442	0,315	14131	0,6	14315	0,247	14454	-0,074
13443	0,3	14132	0,544	14321	0,588	14455	-0,158
13444	0,166	14133	0,529	14322	0,532	14511	0,425
13445	0,027	14134	0,348	14323	0,517	14512	0,369
13451	0,105	14135	0,16	14324	0,337	14513	0,354
13452	0,049	14141	0,414	14325	0,149	14514	0,273
13453	0,034	14142	0,357	14331	0,564	14515	0,189
13454	-0,047	14143	0,343	14332	0,508	14521	0,327
13455	-0,131	14144	0,202	14333	0,493	14522	0,27
13511	0,452	14145	0,055	14334	0,312	14523	0,256
13512	0,396	14151	0,133	14335	0,124	14524	0,175
13513	0,381	14152	0,077	14341	0,378	14525	0,091
13514	0,3	14153	0,062	14342	0,321	14531	0,302
13515	0,216	14154	-0,019	14343	0,307	14532	0,246
13521	0,354	14155	-0,103	14344	0,166	14533	0,231
13522	0,297	14211	0,694	14345	0,019	14534	0,15
13523	0,283	14212	0,638	14351	0,097	14535	0,066
13524	0,202	14213	0,623	14352	0,041	14541	0,197
13525	0,118	14214	0,442	14353	0,026	14542	0,141
13531	0,329	14215	0,254	14354	-0,055	14543	0,126
13532	0,273	14221	0,596	14355	-0,139	14544	0,045
13533	0,258	14222	0,539	14411	0,601	14545	-0,039
13534	0,177	14223	0,525	14412	0,545	14551	0,039
13535	0,093	14224	0,344	14413	0,53	14552	-0,017
13541	0,224	14225	0,156	14414	0,382	14553	-0,032
13542	0,168	14231	0,571	14415	0,228	14554	-0,113
13543	0,153	14232	0,515	14421	0,502	14555	-0,197
13544	0,072	14233	0,5	14422	0,446	15111	0,436
13545	-0,012	14234	0,319	14423	0,431	15112	0,38
13551	0,066	14235	0,131	14424	0,283	15113	0,365
13552	0,01	14241	0,385	14425	0,13	15114	0,284
13553	-0,005	14242	0,328	14431	0,478	15115	0,2
13554	-0,086	14243	0,314	14432	0,422	15121	0,338
13555	-0,17	14244	0,173	14433	0,407	15122	0,281
14111	0,723	14245	0,026	14434	0,259	15123	0,267
14112	0,667	14251	0,104	14435	0,105	15124	0,186
14113	0,652	14252	0,048	14441	0,318	15125	0,102
14114	0,471	14253	0,033	14442	0,262	15131	0,313
14115	0,283	14254	-0,048	14443	0,247	15132	0,257
14121	0,624	14255	-0,132	14444	0,126	15133	0,242
14122	0,568	14311	0,687	14445	0	15134	0,161
14123	0,553	14312	0,631	14451	0,078	15135	0,077
14124	0,373	14313	0,616	14452	0,022	15141	0,208

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
15142	0,152	15331	0,277	21115	0,357	21254	0,026
15143	0,137	15332	0,221	21121	0,767	21255	-0,058
15144	0,056	15333	0,206	21122	0,708	21311	0,826
15145	-0,028	15334	0,125	21123	0,693	21312	0,77
15151	0,05	15335	0,041	21124	0,48	21313	0,755
15152	-0,006	15341	0,172	21125	0,259	21314	0,542
15153	-0,021	15342	0,116	21131	0,739	21315	0,321
15154	-0,102	15343	0,101	21132	0,683	21321	0,728
15155	-0,186	15344	0,02	21133	0,668	21322	0,671
15211	0,407	15345	-0,064	21134	0,455	21323	0,657
15212	0,351	15351	0,014	21135	0,234	21324	0,444
15213	0,336	15352	-0,042	21141	0,527	21325	0,223
15214	0,255	15353	-0,057	21142	0,47	21331	0,703
15215	0,171	15354	-0,138	21143	0,456	21332	0,647
15221	0,309	15355	-0,222	21144	0,296	21333	0,632
15222	0,252	15411	0,381	21145	0,129	21334	0,419
15223	0,238	15412	0,325	21151	0,207	21335	0,198
15224	0,157	15413	0,31	21152	0,151	21341	0,491
15225	0,073	15414	0,229	21153	0,136	21342	0,434
15231	0,284	15415	0,145	21154	0,055	21343	0,42
15232	0,228	15421	0,282	21155	-0,029	21344	0,26
15233	0,213	15422	0,226	21211	0,836	21345	0,093
15234	0,132	15423	0,211	21212	0,778	21351	0,171
15235	0,048	15424	0,13	21213	0,762	21352	0,115
15241	0,179	15425	0,046	21214	0,549	21353	0,1
15242	0,123	15431	0,258	21215	0,328	21354	0,019
15243	0,108	15432	0,202	21221	0,735	21355	-0,065
15244	0,027	15433	0,187	21222	0,679	21411	0,719
15245	-0,057	15434	0,106	21223	0,664	21412	0,663
15251	0,021	15435	0,022	21224	0,451	21413	0,648
15252	-0,035	15441	0,153	21225	0,23	21414	0,478
15253	-0,05	15442	0,097	21231	0,71	21415	0,302
15254	-0,131	15443	0,082	21232	0,654	21421	0,62
15255	-0,215	15544	-0,038	21233	0,639	21422	0,564
15311	0,4	15545	-0,122	21234	0,426	21423	0,549
15312	0,344	15551	-0,044	21235	0,205	21424	0,38
15313	0,329	15552	-0,1	21241	0,498	21425	0,204
15314	0,248	15553	-0,115	21242	0,442	21431	0,596
15315	0,164	15554	-0,196	21243	0,427	21432	0,54
15321	0,302	15555	-0,28	21244	0,267	21433	0,525
15322	0,245	21111	0,877	21245	0,1	21434	0,355
15323	0,231	21112	0,809	21251	0,178	21435	0,179
15324	0,15	21113	0,791	21252	0,122	21441	0,419
15325	0,066	21114	0,578	21253	0,107	21442	0,362

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
21443	0,348	22132	0,596	22321	0,641	22455	-0,17
21444	0,213	22133	0,582	22322	0,585	22511	0,413
21445	0,074	22134	0,369	22323	0,57	22512	0,356
21451	0,152	22135	0,148	22324	0,357	22513	0,342
21452	0,096	22141	0,44	22325	0,136	22514	0,261
21453	0,081	22142	0,384	22331	0,617	22515	0,177
21454	0	22143	0,369	22332	0,56	22521	0,314
21455	-0,084	22144	0,209	22333	0,546	22522	0,258
21511	0,499	22145	0,043	22334	0,333	22523	0,243
21512	0,443	22151	0,121	22335	0,112	22524	0,162
21513	0,428	22152	0,064	22341	0,404	22525	0,078
21514	0,347	22153	0,05	22342	0,348	22531	0,29
21515	0,263	22154	-0,031	22343	0,333	22532	0,233
21521	0,401	22155	-0,115	22344	0,173	22533	0,219
21522	0,344	22211	0,747	22345	0,007	22534	0,138
21523	0,33	22212	0,691	22351	0,085	22535	0,054
21524	0,249	22213	0,676	22352	0,028	22541	0,185
21525	0,165	22214	0,463	22353	0,014	22542	0,128
21531	0,376	22215	0,242	22354	-0,067	22543	0,114
21532	0,32	22221	0,648	22355	-0,151	22544	0,033
21533	0,305	22222	0,592	22411	0,632	22545	-0,051
21534	0,224	22223	0,577	22412	0,576	22551	0,027
21535	0,14	22224	0,364	22413	0,561	22552	-0,03
21541	0,271	22225	0,143	22414	0,392	22553	-0,044
21542	0,215	22231	0,624	22415	0,216	22554	-0,125
21543	0,2	22232	0,567	22421	0,534	22555	-0,209
21544	0,119	22233	0,553	22422	0,477	23111	0,758
21545	0,035	22234	0,34	22423	0,463	23112	0,702
21551	0,113	22235	0,119	22424	0,293	23113	0,687
21552	0,057	22241	0,411	22425	0,117	23114	0,474
21553	0,042	22242	0,355	22431	0,509	23115	0,253
21554	-0,039	22243	0,34	22432	0,453	23121	0,66
21555	-0,123	22244	0,18	22433	0,438	23122	0,603
22111	0,778	22245	0,014	22434	0,269	23123	0,589
22112	0,72	22251	0,092	22435	0,093	23124	0,376
22113	0,705	22252	0,035	22441	0,332	23125	0,155
22114	0,492	22253	0,021	22442	0,276	23131	0,635
22115	0,271	22254	-0,06	22443	0,261	23132	0,579
22121	0,678	22255	-0,144	22444	0,127	23133	0,564
22122	0,621	22311	0,74	22445	-0,013	23134	0,351
22123	0,606	22312	0,683	22451	0,066	23135	0,13
22124	0,393	22313	0,669	22452	0,009	23141	0,423
22125	0,172	22314	0,456	22453	-0,005	23142	0,366
22131	0,653	22315	0,235	22454	-0,086	23143	0,352

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
23144	0,192	23333	0,528	23522	0,24	24155	-0,16
23145	0,025	23334	0,315	23523	0,226	24211	0,637
23151	0,103	23335	0,094	23524	0,145	24212	0,581
23152	0,047	23341	0,387	23525	0,061	24213	0,566
23153	0,032	23342	0,33	23531	0,272	24214	0,385
23154	-0,049	23343	0,316	23532	0,216	24215	0,198
23155	-0,133	23344	0,156	23533	0,201	24221	0,539
23211	0,729	23345	-0,011	23534	0,12	24222	0,482
23212	0,673	23351	0,067	23535	0,036	24223	0,468
23213	0,658	23352	0,011	23541	0,167	24224	0,287
23214	0,445	23353	-0,004	23542	0,111	24225	0,099
23215	0,224	23354	-0,085	23543	0,096	24231	0,514
23221	0,631	23355	-0,169	23544	0,015	24232	0,458
23222	0,575	23411	0,615	23545	-0,069	24233	0,443
23223	0,56	23412	0,559	23551	0,009	24234	0,262
23224	0,347	23413	0,544	23552	-0,047	24235	0,075
23225	0,126	23414	0,374	23553	-0,062	24241	0,328
23231	0,606	23415	0,198	23554	-0,143	24242	0,272
23232	0,55	23421	0,516	23555	-0,227	24243	0,257
23233	0,535	23422	0,46	24111	0,666	24244	0,116
23234	0,322	23423	0,445	24112	0,61	24245	-0,03
23235	0,101	23424	0,276	24113	0,595	24251	0,048
23241	0,394	23425	0,1	24114	0,414	24252	-0,009
23242	0,338	23431	0,492	24115	0,227	24253	-0,023
23243	0,323	23432	0,436	24121	0,568	24254	-0,104
23244	0,163	23433	0,421	24122	0,511	24255	-0,188
23245	-0,004	23434	0,251	24123	0,497	24311	0,63
23251	0,074	23435	0,075	24124	0,316	24312	0,574
23252	0,018	23441	0,315	24125	0,128	24313	0,559
23253	0,003	23442	0,258	24131	0,543	24314	0,378
23254	-0,078	23443	0,244	24132	0,487	24315	0,191
23255	-0,162	23444	0,109	24133	0,472	24321	0,532
23311	0,722	23445	-0,03	24134	0,291	24322	0,475
23312	0,666	23451	0,048	24135	0,104	24323	0,461
23313	0,651	23452	-0,008	24141	0,357	24324	0,28
23314	0,438	23453	-0,023	24142	0,3	24325	0,092
23315	0,217	23454	-0,104	24143	0,286	24331	0,507
23321	0,624	23455	-0,188	24144	0,145	24332	0,451
23322	0,567	23511	0,395	24145	-0,002	24333	0,436
23323	0,553	23512	0,339	24151	0,077	24334	0,255
23324	0,34	23513	0,324	24152	0,02	24335	0,068
23325	0,119	23514	0,243	24153	0,006	24341	0,321
23331	0,599	23515	0,159	24154	-0,076	24342	0,264
23332	0,543	23521	0,297	24155	-0,16	24343	0,25

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
24344	0,109	24533	0,175	25222	0,196	25411	0,324
24345	-0,038	24534	0,094	25223	0,181	25412	0,268
24351	0,041	24535	0,01	25224	0,1	25413	0,253
24352	-0,016	24541	0,14	25225	0,016	25414	0,172
24353	-0,031	24542	0,084	25231	0,227	25415	0,088
24354	-0,112	24543	0,069	25232	0,171	25421	0,226
24355	-0,196	24544	-0,012	25233	0,156	25422	0,169
24411	0,544	24545	-0,096	25234	0,075	25423	0,155
24412	0,488	24551	-0,018	25235	-0,009	25424	0,074
24413	0,473	24552	-0,074	25241	0,122	25425	-0,01
24414	0,325	24553	-0,089	25242	0,066	25431	0,201
24415	0,172	24554	-0,17	25243	0,051	25432	0,145
24421	0,446	24555	-0,254	25244	-0,03	25433	0,13
24422	0,389	25111	0,379	25245	-0,114	25434	0,049
24423	0,375	25112	0,323	25251	-0,036	25435	-0,035
24424	0,227	25113	0,308	25252	-0,092	25441	0,096
24425	0,073	25114	0,227	25253	-0,107	25442	0,04
24431	0,421	25115	0,143	25254	-0,188	25443	0,025
24432	0,365	25121	0,281	25255	-0,272	25444	-0,056
24433	0,35	25122	0,224	25311	0,343	25445	-0,14
24434	0,202	25123	0,21	25312	0,287	25451	-0,062
24435	0,049	25124	0,129	25313	0,272	25452	-0,118
24441	0,262	25125	0,045	25314	0,191	25453	-0,133
24442	0,205	25131	0,256	25315	0,107	25454	-0,214
24443	0,191	25132	0,2	25321	0,245	25455	-0,298
24444	0,069	25133	0,185	25322	0,188	25511	0,285
24445	-0,057	25134	0,104	25323	0,174	25512	0,229
24451	0,022	25135	0,02	25324	0,093	25513	0,214
24452	-0,035	25141	0,151	25325	0,009	25514	0,133
24453	-0,05	25142	0,095	25331	0,22	25515	0,049
24454	-0,131	25143	0,08	25332	0,164	25521	0,187
24455	-0,215	25144	-0,001	25333	0,149	25522	0,13
24511	0,369	25145	-0,085	25334	0,068	25523	0,116
24512	0,312	25151	-0,007	25335	-0,016	25524	0,035
24513	0,298	25152	-0,063	25341	0,115	25525	-0,049
24514	0,217	25153	-0,078	25342	0,059	25531	0,162
24515	0,133	25154	-0,159	25343	0,044	25532	0,106
24521	0,27	25155	-0,243	25344	-0,037	25533	0,091
24522	0,214	25211	0,35	25345	-0,121	25534	0,01
24523	0,199	25212	0,294	25351	-0,043	25535	-0,074
24524	0,118	25213	0,279	25352	-0,099	25541	0,057
24525	0,034	25214	0,198	25353	-0,114	25542	0,001
24531	0,246	25215	0,114	25354	-0,195	25543	-0,014
24532	0,189	25221	0,252	25355	-0,279	25544	-0,095

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
25545	-0,179	31234	0,414	31423	0,537	32112	0,707
25551	-0,101	31235	0,193	31424	0,368	32113	0,692
25552	-0,157	31241	0,486	31425	0,191	32114	0,479
25553	-0,172	31242	0,429	31431	0,584	32115	0,258
25554	-0,253	31243	0,415	31432	0,527	32121	0,665
25555	-0,337	31244	0,254	31433	0,513	32122	0,609
31111	0,85	31245	0,088	31434	0,343	32123	0,594
31112	0,794	31251	0,166	31435	0,167	32124	0,381
31113	0,779	31252	0,11	31441	0,406	32125	0,16
31114	0,566	31253	0,095	31442	0,35	32131	0,64
31115	0,345	31254	0,014	31443	0,335	32132	0,584
31121	0,752	31255	-0,07	31444	0,201	32133	0,569
31122	0,695	31311	0,814	31445	0,062	32134	0,356
31123	0,681	31312	0,758	31451	0,14	32135	0,135
31124	0,468	31313	0,743	31452	0,084	32141	0,428
31125	0,247	31314	0,53	31453	0,069	32142	0,372
31131	0,727	31315	0,309	31454	-0,012	32143	0,357
31132	0,671	31321	0,716	31455	-0,096	32144	0,197
31133	0,656	31322	0,659	31511	0,487	32145	0,03
31134	0,443	31323	0,645	31512	0,431	32151	0,108
31135	0,222	31324	0,432	31513	0,416	32152	0,052
31141	0,515	31325	0,211	31514	0,335	32153	0,037
31142	0,458	31331	0,691	31515	0,251	32154	-0,044
31143	0,444	31332	0,635	31521	0,389	32155	-0,128
31144	0,283	31333	0,62	31522	0,332	32211	0,735
31145	0,117	31334	0,407	31523	0,318	32212	0,678
31151	0,195	31335	0,186	31524	0,237	32213	0,664
31152	0,139	31341	0,479	31525	0,153	32214	0,451
31153	0,124	31342	0,422	31531	0,364	32215	0,23
31154	0,043	31343	0,408	31532	0,308	32221	0,636
31155	-0,041	31344	0,247	31533	0,293	32222	0,58
31211	0,821	31345	0,081	31534	0,212	32223	0,565
31212	0,765	31351	0,159	31535	0,128	32224	0,352
31213	0,75	31352	0,103	31541	0,259	32225	0,131
31214	0,537	31353	0,088	31542	0,203	32231	0,612
31215	0,316	31354	0,007	31543	0,188	32232	0,555
31221	0,723	31355	-0,077	31544	0,107	32233	0,541
31222	0,666	31411	0,707	31545	0,023	32234	0,328
31223	0,652	31412	0,65	31551	0,101	32235	0,107
31224	0,439	31413	0,636	31552	0,045	32241	0,399
31225	0,218	31414	0,466	31553	0,03	32242	0,343
31231	0,698	31415	0,29	31554	-0,051	32243	0,328
31232	0,642	31421	0,608	31555	-0,135	32244	0,168
31233	0,627	31422	0,552	32111	0,763	32245	0,002

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
32251	0,08	32435	0,08	33124	0,364	33313	0,639
32252	0,023	32441	0,32	33125	0,143	33314	0,426
32253	0,009	32442	0,263	33131	0,623	33315	0,205
32254	-0,072	32443	0,249	33132	0,567	33321	0,612
32255	-0,157	32444	0,115	33133	0,552	33322	0,555
32311	0,727	32445	-0,025	33134	0,339	33323	0,541
32312	0,671	32451	0,053	33135	0,118	33324	0,328
32313	0,656	32452	-0,003	33141	0,411	33325	0,107
32314	0,443	32453	-0,018	33142	0,354	33331	0,587
32315	0,222	32454	-0,099	33143	0,34	33332	0,531
32321	0,629	32455	-0,183	33144	0,179	33333	0,516
32322	0,573	32511	0,4	33145	0,013	33334	0,303
32323	0,558	32512	0,344	33151	0,091	33335	0,082
32324	0,345	32513	0,329	33152	0,035	33341	0,375
32325	0,124	32514	0,248	33153	0,02	33342	0,318
32331	0,604	32515	0,164	33154	-0,061	33343	0,304
32332	0,548	32521	0,302	33155	-0,145	33344	0,143
32333	0,533	32522	0,246	33211	0,717	33345	-0,023
32334	0,32	32523	0,231	33212	0,661	33351	0,055
32335	0,099	32524	0,15	33213	0,646	33352	-0,001
32341	0,392	32525	0,066	33214	0,433	33353	-0,016
32342	0,336	32531	0,277	33215	0,212	33354	-0,097
32343	0,321	32532	0,221	33221	0,619	33355	-0,181
32344	0,161	32533	0,206	33222	0,562	33411	0,603
32345	-0,006	32534	0,125	33223	0,548	33412	0,546
32351	0,072	32535	0,041	33224	0,335	33413	0,532
32352	0,016	32541	0,172	33225	0,114	33414	0,362
32353	0,001	32542	0,116	33231	0,594	33415	0,186
32354	-0,08	32543	0,101	33232	0,538	33421	0,504
32355	-0,164	32544	0,02	33233	0,523	33422	0,448
32411	0,62	32545	-0,064	33234	0,31	33423	0,433
32412	0,564	32551	0,014	33235	0,089	33424	0,264
32413	0,549	32552	-0,042	33241	0,382	33425	0,087
32414	0,379	32553	-0,057	33242	0,325	33431	0,48
32415	0,203	32554	-0,138	33243	0,311	33432	0,423
32421	0,522	32555	-0,222	33244	0,15	33433	0,409
32422	0,465	33111	0,746	33245	-0,016	33434	0,239
32423	0,451	33112	0,69	33251	0,062	33435	0,063
32424	0,281	33113	0,675	33252	0,006	33441	0,302
32425	0,105	33114	0,462	33253	-0,009	33442	0,246
32431	0,497	33115	0,241	33254	-0,09	33443	0,231
32432	0,441	33121	0,648	33255	-0,174	33444	0,097
32433	0,426	33122	0,591	33311	0,71	33445	-0,042
32434	0,256	33123	0,577	33312	0,654	33451	0,036

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
33452	-0,02	34141	0,345	34325	0,08	34514	0,204
33453	-0,035	34142	0,288	34331	0,495	34515	0,12
33454	-0,116	34143	0,274	34332	0,439	34521	0,258
33455	-0,2	34144	0,133	34333	0,424	34522	0,201
33511	0,383	34145	-0,014	34334	0,243	34523	0,187
33512	0,327	34151	0,064	34335	0,055	34524	0,106
33513	0,312	34152	0,008	34341	0,309	34525	0,022
33514	0,231	34153	-0,007	34342	0,252	34531	0,233
33515	0,147	34154	-0,088	34343	0,238	34532	0,177
33521	0,285	34155	-0,172	34344	0,097	34533	0,162
33522	0,228	34211	0,625	34345	-0,05	34534	0,081
33523	0,214	34212	0,569	34351	0,028	34535	-0,003
33524	0,133	34213	0,554	34352	-0,028	34541	0,128
33525	0,049	34214	0,373	34353	-0,043	34542	0,072
33531	0,26	34215	0,185	34354	-0,124	34543	0,057
33532	0,204	34221	0,527	34355	-0,208	34544	-0,024
33533	0,189	34222	0,47	34411	0,532	34545	-0,108
33534	0,108	34223	0,456	34412	0,476	34551	-0,03
33535	0,024	34224	0,275	34413	0,461	34552	-0,086
33541	0,155	34225	0,087	34414	0,313	34553	-0,101
33542	0,099	34231	0,502	34415	0,159	34554	-0,182
33543	0,084	34232	0,446	34421	0,433	34555	-0,266
33544	0,003	34233	0,431	34422	0,377	35111	0,367
33545	-0,081	34234	0,25	34423	0,362	35112	0,311
33551	-0,003	34235	0,062	34424	0,214	35113	0,296
33552	-0,059	34241	0,316	34425	0,061	35114	0,215
33553	-0,074	34242	0,259	34431	0,409	35115	0,131
33554	-0,155	34243	0,245	34432	0,353	35121	0,269
33555	-0,239	34244	0,104	34433	0,338	35122	0,212
34111	0,654	34245	-0,043	34434	0,19	35123	0,198
34112	0,598	34251	0,035	34435	0,036	35124	0,117
34113	0,583	34252	-0,021	34441	0,249	35125	0,033
34114	0,402	34253	-0,036	34442	0,193	35131	0,244
34115	0,214	34254	-0,117	34443	0,178	35132	0,188
34121	0,555	34255	-0,201	34444	0,057	35133	0,173
34122	0,499	34311	0,618	34445	-0,069	35134	0,092
34123	0,484	34312	0,562	34451	0,009	35135	0,008
34124	0,304	34313	0,547	34452	-0,047	35141	0,139
34125	0,116	34314	0,366	34453	-0,062	35142	0,083
34131	0,531	34315	0,178	34454	-0,143	35143	0,068
34132	0,475	34321	0,519	34455	-0,227	35144	-0,013
34133	0,46	34322	0,463	34511	0,356	35145	-0,097
34134	0,279	34323	0,448	34512	0,3	35151	-0,019
34135	0,091	34324	0,268	34513	0,285	35152	-0,075

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
35153	-0,09	35342	0,047	35531	0,15	41215	0,299
35154	-0,171	35343	0,032	35532	0,094	41221	0,686
35155	-0,255	35344	-0,049	35533	0,079	41222	0,629
35211	0,338	35345	-0,133	35534	-0,002	41223	0,615
35212	0,282	35351	-0,055	35535	-0,086	41224	0,411
35213	0,267	35352	-0,111	35541	0,045	41225	0,2
35214	0,186	35353	-0,126	35542	-0,011	41231	0,661
35215	0,102	35354	-0,207	35543	-0,026	41232	0,605
35221	0,24	35355	-0,291	35544	-0,107	41233	0,59
35222	0,183	35411	0,312	35545	-0,191	41234	0,387
35223	0,169	35412	0,256	35551	-0,113	41235	0,176
35224	0,088	35413	0,241	35552	-0,169	41241	0,456
35225	0,004	35414	0,16	35553	-0,184	41242	0,4
35231	0,215	35415	0,076	35554	-0,265	41243	0,385
35232	0,159	35421	0,213	35555	-0,349	41244	0,231
35233	0,144	35422	0,157	41111	0,813	41245	0,07
35234	0,063	35423	0,142	41112	0,757	41251	0,149
35235	-0,021	35424	0,061	41113	0,742	41252	0,092
35241	0,11	35425	-0,023	41114	0,539	41253	0,078
35242	0,054	35431	0,189	41115	0,327	41254	-0,004
35243	0,039	35432	0,133	41121	0,714	41255	-0,088
35244	-0,042	35433	0,118	41122	0,658	41311	0,777
35245	-0,126	35434	0,037	41123	0,643	41312	0,721
35251	-0,048	35435	-0,047	41124	0,44	41313	0,706
35252	-0,104	35441	0,084	41125	0,229	41314	0,503
35253	-0,119	35442	0,028	41131	0,69	41315	0,291
35254	-0,2	35443	0,013	41132	0,634	41321	0,678
35255	-0,284	35444	-0,068	41133	0,619	41322	0,622
35311	0,331	35445	-0,152	41134	0,416	41323	0,607
35312	0,275	35451	-0,074	41135	0,204	41324	0,404
35313	0,26	35452	-0,13	41141	0,485	41325	0,193
35314	0,179	35453	-0,145	41142	0,429	41331	0,654
35315	0,095	35454	-0,226	41143	0,414	41332	0,598
35321	0,233	35455	-0,31	41144	0,26	41333	0,583
35322	0,176	35511	0,273	41145	0,099	41334	0,38
35323	0,162	35512	0,217	41151	0,177	41335	0,168
35324	0,081	35513	0,202	41152	0,121	41341	0,449
35325	-0,004	35514	0,121	41153	0,106	41342	0,393
35331	0,208	35515	0,037	41154	0,025	41343	0,378
35332	0,152	35521	0,175	41155	-0,059	41344	0,224
35333	0,137	35522	0,118	41211	0,784	41345	0,063
35334	0,056	35523	0,104	41212	0,728	41351	0,141
35335	-0,028	35524	0,023	41213	0,713	41352	0,085
35341	0,103	35525	-0,062	41214	0,51	41353	0,07

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
41354	-0,011	41543	0,17	42232	0,518	42421	0,491
41355	-0,095	41544	0,089	42233	0,504	42422	0,434
41411	0,676	41545	0,005	42234	0,3	42423	0,42
41412	0,62	41551	0,083	42235	0,089	42424	0,257
41413	0,605	41552	0,027	42241	0,37	42425	0,087
41414	0,442	41553	0,012	42242	0,313	42431	0,466
41415	0,272	41554	-0,069	42243	0,299	42432	0,41
41421	0,577	41555	-0,153	42244	0,144	42433	0,395
41422	0,521	42111	0,726	42245	-0,016	42434	0,232
41423	0,506	42112	0,67	42251	0,062	42435	0,063
41424	0,343	42113	0,655	42252	0,006	42441	0,294
41425	0,174	42114	0,452	42253	-0,009	42442	0,238
41431	0,553	42115	0,241	42254	-0,09	42443	0,223
41432	0,497	42121	0,628	42255	-0,174	42444	0,093
41433	0,482	42122	0,572	42311	0,69	42445	-0,042
41434	0,319	42123	0,557	42312	0,634	42451	0,036
41435	0,149	42124	0,353	42313	0,619	42452	-0,021
41441	0,381	42125	0,142	42314	0,416	42453	-0,035
41442	0,325	42131	0,603	42315	0,205	42454	-0,116
41443	0,31	42132	0,547	42321	0,592	42455	-0,2
41444	0,18	42133	0,532	42322	0,536	42511	0,383
41445	0,044	42134	0,329	42323	0,521	42512	0,326
41451	0,122	42135	0,118	42324	0,317	42513	0,312
41452	0,066	42141	0,399	42325	0,106	42514	0,231
41453	0,051	42142	0,342	42331	0,567	42515	0,147
41454	-0,03	42143	0,328	42332	0,511	42521	0,284
41455	-0,114	42144	0,173	42333	0,496	42522	0,228
41511	0,469	42145	0,013	42334	0,293	42523	0,213
41512	0,413	42151	0,091	42335	0,082	42524	0,132
41513	0,398	42152	0,034	42341	0,363	42525	0,048
41514	0,317	42153	0,02	42342	0,306	42531	0,26
41515	0,233	42154	-0,061	42343	0,292	42532	0,203
41521	0,371	42155	-0,145	42344	0,137	42533	0,189
41522	0,315	42211	0,698	42345	-0,023	42534	0,108
41523	0,3	42212	0,641	42351	0,055	42535	0,024
41524	0,219	42213	0,627	42352	-0,002	42541	0,155
41525	0,135	42214	0,423	42353	-0,016	42542	0,098
41531	0,346	42215	0,212	42354	-0,097	42543	0,084
41532	0,29	42221	0,599	42355	-0,181	42544	0,003
41533	0,275	42222	0,543	42411	0,589	42545	-0,081
41534	0,194	42223	0,528	42412	0,533	42551	-0,003
41535	0,11	42224	0,325	42413	0,518	42552	-0,06
41541	0,241	42225	0,113	42414	0,355	42553	-0,074
41542	0,185	42231	0,575	42415	0,186	42554	-0,155

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
42555	-0,239	43244	0,127	43433	0,378	44122	0,467
43111	0,709	43245	-0,034	43434	0,215	44123	0,452
43112	0,653	43251	0,045	43435	0,045	44124	0,278
43113	0,638	43252	-0,012	43441	0,277	44125	0,098
43114	0,435	43253	-0,027	43442	0,221	44131	0,499
43115	0,223	43254	-0,108	43443	0,206	44132	0,442
43121	0,61	43255	-0,192	43444	0,076	44133	0,428
43122	0,554	43311	0,673	43445	-0,06	44134	0,254
43123	0,539	43312	0,617	43451	0,018	44135	0,074
43124	0,336	43313	0,602	43452	-0,038	44141	0,318
43125	0,125	43314	0,399	43453	-0,053	44142	0,262
43131	0,586	43315	0,187	43454	-0,134	44143	0,247
43132	0,53	43321	0,574	43455	-0,218	44144	0,11
43133	0,515	43322	0,518	43511	0,365	44145	-0,032
43134	0,312	43323	0,503	43512	0,309	44151	0,047
43135	0,1	43324	0,3	43513	0,294	44152	-0,01
43141	0,381	43325	0,089	43514	0,213	44153	-0,024
43142	0,325	43331	0,55	43515	0,129	44154	-0,105
43143	0,31	43332	0,494	43521	0,267	44155	-0,189
43144	0,156	43333	0,479	43522	0,211	44211	0,593
43145	-0,005	43334	0,276	43523	0,196	44212	0,536
43151	0,073	43335	0,064	43524	0,115	44213	0,522
43152	0,017	43341	0,345	43525	0,031	44214	0,348
43153	0,002	43342	0,289	43531	0,242	44215	0,168
43154	-0,079	43343	0,274	43532	0,186	44221	0,494
43155	-0,163	43344	0,12	43533	0,171	44222	0,438
43211	0,68	43345	-0,041	43534	0,09	44223	0,423
43212	0,624	43351	0,037	43535	0,006	44224	0,249
43213	0,609	43352	-0,019	43541	0,137	44225	0,069
43214	0,406	43353	-0,034	43542	0,081	44231	0,47
43215	0,195	43354	-0,115	43543	0,066	44232	0,413
43221	0,582	43355	-0,199	43544	-0,015	44233	0,399
43222	0,525	43411	0,572	43545	-0,099	44234	0,225
43223	0,511	43412	0,516	43551	-0,021	44235	0,045
43224	0,307	43413	0,501	43552	-0,077	44241	0,289
43225	0,096	43414	0,338	43553	-0,092	44242	0,233
43231	0,557	43415	0,168	43554	-0,173	44243	0,218
43232	0,501	43421	0,473	43555	-0,257	44244	0,082
43233	0,486	43422	0,417	44111	0,622	44245	-0,06
43234	0,283	43423	0,402	44112	0,565	44251	0,018
43235	0,072	43424	0,239	44113	0,551	44252	-0,039
43241	0,352	43425	0,07	44114	0,377	44253	-0,053
43242	0,296	43431	0,449	44115	0,197	44254	-0,134
43243	0,281	43432	0,393	44121	0,523	44255	-0,218

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
44311	0,586	44445	-0,087	45134	0,074	45323	0,144
44312	0,529	44451	-0,009	45135	-0,01	45324	0,063
44313	0,515	44452	-0,065	45141	0,121	45325	-0,021
44314	0,341	44453	-0,08	45142	0,065	45331	0,19
44315	0,161	44454	-0,16	45143	0,05	45332	0,134
44321	0,487	44455	-0,245	45144	-0,031	45333	0,119
44322	0,431	44511	0,339	45145	-0,115	45334	0,038
44323	0,416	44512	0,282	45151	-0,037	45335	-0,046
44324	0,242	44513	0,268	45152	-0,093	45341	0,085
44325	0,062	44514	0,187	45153	-0,108	45342	0,029
44331	0,463	44515	0,103	45154	-0,189	45343	0,014
44332	0,406	44521	0,24	45155	-0,273	45344	-0,067
44333	0,392	44522	0,184	45211	0,321	45345	-0,151
44334	0,218	44523	0,169	45212	0,264	45351	-0,073
44335	0,038	44524	0,088	45213	0,25	45352	-0,129
44341	0,282	44525	0,004	45214	0,169	45353	-0,144
44342	0,226	44531	0,216	45215	0,085	45354	-0,225
44343	0,211	44532	0,159	45221	0,222	45355	-0,309
44344	0,074	44533	0,145	45222	0,166	45411	0,294
44345	-0,068	44534	0,064	45223	0,151	45412	0,238
44351	0,011	44535	-0,02	45224	0,07	45413	0,223
44352	-0,046	44541	0,111	45225	-0,014	45414	0,142
44353	-0,06	44542	0,054	45231	0,198	45415	0,058
44354	-0,141	44543	0,04	45232	0,141	45421	0,196
44355	-0,225	44544	-0,041	45233	0,127	45422	0,139
44411	0,504	44545	-0,126	45234	0,046	45423	0,125
44412	0,448	44551	-0,047	45235	-0,039	45424	0,044
44413	0,433	44552	-0,104	45241	0,092	45425	-0,04
44414	0,29	44553	-0,118	45242	0,036	45431	0,171
44415	0,142	44554	-0,199	45243	0,021	45432	0,115
44421	0,406	44555	-0,283	45244	-0,06	45433	0,1
44422	0,35	45111	0,349	45245	-0,144	45434	0,019
44423	0,335	45112	0,293	45251	-0,066	45435	-0,065
44424	0,192	45113	0,278	45252	-0,122	45441	0,066
44425	0,043	45114	0,197	45253	-0,137	45442	0,01
44431	0,381	45115	0,113	45254	-0,218	45443	-0,005
44432	0,325	45121	0,251	45255	-0,302	45444	-0,086
44433	0,31	45122	0,195	45311	0,313	45445	-0,17
44434	0,167	45123	0,18	45312	0,257	45451	-0,092
44435	0,019	45124	0,099	45313	0,242	45452	-0,148
44441	0,226	45125	0,015	45314	0,161	45453	-0,163
44442	0,169	45131	0,226	45315	0,077	45454	-0,244
44443	0,155	45132	0,17	45321	0,215	45455	-0,328
44444	0,036	45133	0,155	45322	0,159	45511	0,255

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
45512	0,199	51151	-0,05	51335	-0,059	51524	-0,009
45513	0,184	51152	-0,106	51341	0,072	51525	-0,093
45514	0,103	51153	-0,121	51342	0,016	51531	0,119
45515	0,019	51154	-0,202	51343	0,001	51532	0,063
45521	0,157	51155	-0,286	51344	-0,08	51533	0,048
45522	0,101	51211	0,307	51345	-0,164	51534	-0,033
45523	0,086	51212	0,251	51351	-0,086	51535	-0,117
45524	0,005	51213	0,236	51352	-0,142	51541	0,014
45525	-0,079	51214	0,155	51353	-0,157	51542	-0,042
45531	0,132	51215	0,071	51354	-0,238	51543	-0,057
45532	0,076	51221	0,209	51355	-0,322	51544	-0,138
45533	0,061	51222	0,152	51411	0,281	51545	-0,222
45534	-0,02	51223	0,138	51412	0,225	51551	-0,144
45535	-0,104	51224	0,057	51413	0,21	51552	-0,2
45541	0,027	51225	-0,027	51414	0,129	51553	-0,215
45542	-0,029	51231	0,184	51415	0,045	51554	-0,296
45543	-0,044	51232	0,128	51421	0,182	51555	-0,38
45544	-0,125	51233	0,113	51422	0,126	52111	0,249
45545	-0,209	51234	0,032	51423	0,111	52112	0,193
45551	-0,131	51235	-0,052	51424	0,03	52113	0,178
45552	-0,187	51241	0,079	51425	-0,054	52114	0,097
45553	-0,202	51242	0,023	51431	0,158	52115	0,013
45554	-0,283	51243	0,008	51432	0,102	52121	0,151
45555	-0,367	51244	-0,073	51433	0,087	52122	0,095
51111	0,336	51245	-0,157	51434	0,006	52123	0,08
51112	0,28	51251	-0,079	51435	-0,078	52124	-0,001
51113	0,265	51252	-0,135	51441	0,053	52125	-0,085
51114	0,184	51253	-0,15	51442	-0,003	52131	0,126
51115	0,1	51254	-0,231	51443	-0,018	52132	0,07
51121	0,238	51255	-0,315	51444	-0,099	52133	0,055
51122	0,181	51311	0,3	51445	-0,183	52134	-0,026
51123	0,167	51312	0,244	51451	-0,105	52135	-0,11
51124	0,086	51313	0,229	51452	-0,161	52141	0,021
51125	0,002	51314	0,148	51453	-0,176	52142	-0,035
51131	0,213	51315	0,064	51454	-0,257	52143	-0,05
51132	0,157	51321	0,202	51455	-0,341	52144	-0,131
51133	0,142	51322	0,145	51511	0,242	52145	-0,215
51134	0,061	51323	0,131	51512	0,186	52151	-0,137
51135	-0,023	51324	0,05	51513	0,171	52152	-0,193
51141	0,108	51325	-0,035	51514	0,09	52153	-0,208
51142	0,052	51331	0,177	51515	0,006	52154	-0,289
51143	0,037	51332	0,121	51521	0,144	52155	-0,373
51144	-0,044	51333	0,106	51522	0,087	52211	0,221
51145	-0,128	51334	0,025	51523	0,073	52212	0,164

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52213	0,15	52352	-0,229	52541	-0,073	53225	-0,131
52214	0,069	52353	-0,244	52542	-0,129	53231	0,08
52215	-0,016	52354	-0,325	52543	-0,144	53232	0,024
52221	0,122	52355	-0,409	52544	-0,225	53233	0,009
52222	0,066	52411	0,194	52545	-0,309	53234	-0,072
52223	0,051	52412	0,138	52551	-0,231	53235	-0,156
52224	-0,03	52413	0,123	52552	-0,287	53241	-0,025
52225	-0,114	52414	0,042	52553	-0,302	53242	-0,081
52231	0,098	52415	-0,042	52554	-0,383	53243	-0,096
52232	0,041	52421	0,096	52555	-0,467	53244	-0,177
52233	0,027	52422	0,04	53111	0,232	53245	-0,261
52234	-0,054	52423	0,025	53112	0,176	53251	-0,183
52235	-0,139	52424	-0,056	53113	0,161	53252	-0,239
52241	-0,008	52425	-0,14	53114	0,08	53253	-0,254
52242	-0,064	52431	0,071	53115	-0,004	53254	-0,335
52243	-0,079	52432	0,015	53121	0,134	53255	-0,419
52244	-0,16	52433	0	53122	0,077	53311	0,196
52245	-0,244	52434	-0,081	53123	0,063	53312	0,14
52251	-0,166	52435	-0,165	53124	-0,019	53313	0,125
52252	-0,222	52441	-0,034	53125	-0,103	53314	0,044
52253	-0,237	52442	-0,09	53131	0,109	53315	-0,04
52254	-0,317	52443	-0,105	53132	0,053	53321	0,098
52255	-0,402	52444	-0,186	53133	0,038	53322	0,041
52311	0,213	52445	-0,27	53134	-0,043	53323	0,027
52312	0,157	52451	-0,192	53135	-0,127	53324	-0,055
52313	0,142	52452	-0,248	53141	0,004	53325	-0,139
52314	0,061	52453	-0,263	53142	-0,052	53331	0,073
52315	-0,023	52454	-0,344	53143	-0,067	53332	0,017
52321	0,115	52455	-0,428	53144	-0,148	53333	0,002
52322	0,059	52511	0,155	53145	-0,232	53334	-0,079
52323	0,044	52512	0,099	53151	-0,154	53335	-0,163
52324	-0,037	52513	0,084	53152	-0,21	53341	-0,032
52325	-0,121	52514	0,003	53153	-0,225	53342	-0,088
52331	0,09	52515	-0,081	53154	-0,306	53343	-0,103
52332	0,034	52521	0,057	53155	-0,39	53344	-0,184
52333	0,019	52522	0,001	53211	0,203	53345	-0,268
52334	-0,062	52523	-0,014	53212	0,147	53351	-0,19
52335	-0,146	52524	-0,095	53213	0,132	53352	-0,246
52341	-0,015	52525	-0,179	53214	0,051	53353	-0,261
52342	-0,071	52531	0,032	53215	-0,033	53354	-0,342
52343	-0,086	52532	-0,024	53221	0,105	53355	-0,426
52344	-0,167	52533	-0,039	53222	0,048	53411	0,177
52345	-0,251	52534	-0,12	53223	0,034	53412	0,121
52351	-0,173	52535	-0,204	53224	-0,047	53413	0,106

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
53414	0,025	53553	-0,319	54242	-0,108	54431	0,027
53415	-0,059	53554	-0,4	54243	-0,123	54432	-0,029
53421	0,078	53555	-0,484	54244	-0,204	54433	-0,044
53422	0,022	54111	0,205	54245	-0,288	54434	-0,125
53423	0,007	54112	0,149	54251	-0,21	54435	-0,209
53424	-0,074	54113	0,134	54252	-0,266	54441	-0,078
53425	-0,158	54114	0,053	54253	-0,281	54442	-0,134
53431	0,054	54115	-0,031	54254	-0,362	54443	-0,149
53432	-0,002	54121	0,107	54255	-0,446	54444	-0,23
53433	-0,017	54122	0,05	54311	0,169	54445	-0,314
53434	-0,098	54123	0,036	54312	0,113	54451	-0,236
53435	-0,182	54124	-0,045	54313	0,098	54452	-0,292
53441	-0,051	54125	-0,129	54314	0,017	54453	-0,307
53442	-0,107	54131	0,082	54315	-0,067	54454	-0,388
53443	-0,122	54132	0,026	54321	0,071	54455	-0,472
53444	-0,203	54133	0,011	54322	0,014	54511	0,111
53445	-0,287	54134	-0,07	54323	0	54512	0,055
53451	-0,209	54135	-0,154	54324	-0,081	54513	0,04
53452	-0,265	54141	-0,023	54325	-0,165	54514	-0,041
53453	-0,28	54142	-0,079	54331	0,046	54515	-0,125
53454	-0,361	54143	-0,094	54332	-0,01	54521	0,013
53455	-0,445	54144	-0,175	54333	-0,025	54522	-0,044
53511	0,138	54145	-0,259	54334	-0,106	54523	-0,058
53512	0,082	54151	-0,181	54335	-0,19	54524	-0,139
53513	0,067	54152	-0,237	54341	-0,059	54525	-0,223
53514	-0,014	54153	-0,252	54342	-0,115	54531	-0,012
53515	-0,098	54154	-0,333	54343	-0,13	54532	-0,068
53521	0,04	54155	-0,417	54344	-0,211	54533	-0,083
53522	-0,017	54211	0,176	54345	-0,295	54534	-0,164
53523	-0,032	54212	0,12	54351	-0,217	54535	-0,248
53524	-0,113	54213	0,105	54352	-0,273	54541	-0,117
53525	-0,197	54214	0,024	54353	-0,288	54542	-0,173
53531	0,015	54215	-0,06	54354	-0,369	54543	-0,188
53532	-0,041	54221	0,078	54355	-0,453	54544	-0,269
53533	-0,056	54222	0,022	54411	0,15	54545	-0,353
53534	-0,137	54223	0,007	54412	0,094	54551	-0,275
53535	-0,221	54224	-0,074	54413	0,079	54552	-0,331
53541	-0,09	54225	-0,158	54414	-0,002	54553	-0,346
53542	-0,146	54231	0,053	54415	-0,086	54554	-0,427
53543	-0,161	54232	-0,003	54421	0,052	54555	-0,511
53544	-0,242	54233	-0,018	54422	-0,005	55111	0,122
53545	-0,326	54234	-0,099	54423	-0,019	55112	0,066
53551	-0,248	54235	-0,183	54424	-0,1	55113	0,051
53552	-0,304	54241	-0,052	54425	-0,184	55114	-0,03

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
55115	-0,114	55254	-0,445	55443	-0,232		
55121	0,024	55255	-0,529	55444	-0,313		
55122	-0,033	55311	0,086	55445	-0,397		
55123	-0,048	55312	0,03	55451	-0,319		
55124	-0,129	55313	0,015	55452	-0,375		
55125	-0,213	55314	-0,066	55453	-0,39		
55131	-0,001	55315	-0,15	55454	-0,471		
55132	-0,057	55321	-0,013	55455	-0,555		
55133	-0,072	55322	-0,069	55511	0,028		
55134	-0,153	55323	-0,084	55512	-0,028		
55135	-0,237	55324	-0,165	55513	-0,043		
55141	-0,106	55325	-0,249	55514	-0,124		
55142	-0,162	55331	-0,037	55515	-0,208		
55143	-0,177	55332	-0,093	55521	-0,071		
55144	-0,258	55333	-0,108	55522	-0,127		
55145	-0,342	55334	-0,189	55523	-0,142		
55151	-0,264	55335	-0,273	55524	-0,223		
55152	-0,32	55341	-0,142	55525	-0,307		
55153	-0,335	55342	-0,198	55531	-0,095		
55154	-0,416	55343	-0,213	55532	-0,151		
55155	-0,5	55344	-0,294	55533	-0,166		
55211	0,093	55345	-0,378	55534	-0,247		
55212	0,037	55351	-0,3	55535	-0,331		
55213	0,022	55352	-0,356	55541	-0,2		
55214	-0,059	55353	-0,371	55542	-0,256		
55215	-0,143	55354	-0,452	55543	-0,271		
55221	-0,005	55355	-0,536	55544	-0,352		
55222	-0,062	55411	0,067	55545	-0,436		
55223	-0,076	55412	0,011	55551	-0,358		
55224	-0,157	55413	-0,004	55552	-0,414		
55225	-0,241	55414	-0,085	55553	-0,429		
55231	-0,03	55415	-0,169	55554	-0,51		
55232	-0,086	55421	-0,032	55555	-0,594		
55233	-0,101	55422	-0,088				
55234	-0,182	55423	-0,103				
55235	-0,266	55424	-0,184				
55241	-0,135	55425	-0,268				
55242	-0,191	55431	-0,056				
55243	-0,206	55432	-0,112				
55244	-0,287	55433	-0,127				
55245	-0,371	55434	-0,208				
55251	-0,293	55435	-0,292				
55252	-0,349	55441	-0,161				
55253	-0,364	55442	-0,217				

ATTACHMENT 6. : HRS DERIVATION

The HRS categories should be evaluated from 6 to 1. First check if the subject falls in category 6 (has the subject died?) if not then we evaluate category 5, if not 5 then evaluate category 4 and so on.
The HRS is evaluated at baseline and per day, relative to the first study drug intake.
The baseline HRS is covering the full baseline/screening/day 1 visit which can occur on 2 days.
Timing of first study drug intake is not taken into account.

Note:

- VSOXYSAT is assessed 3 times per day (or per baseline visit). In case one of the assessments says 'N' then the final result for that day (or baseline visit) is 'N', else if one of the assessments is 'NA' then the final result is 'NA' else if one of the assessments is missing then final result is missing.
  So a combination of 'Y', "", "N" ➔ result ='N'
  'Y', "", "NA" ➔ result ='NA'
  'Y;'Y','' ➔ result =''
  'Y;'Y','Y' ➔ result ='Y'
  On the baseline visit, on days at or after HO end date or on the day of discontinuation it might be that less than 3 assessments are done. Therefore, take only the records into account from the dataset on those days as planned. The same rules above apply to derive the final result per day when more than 1 assessment is collected.

- In case the subject withdrew from the study, the HRS will be set to missing from the next day onwards.
- In case of chronic oxygen use and multiple CMARTN values on a day we consider the worst value: In case one of the values is 'N' then final result for that day (or baseline visit) is 'N', else if one of the assessments is missing then final result is missing.
- The list of types of supplemental oxygen and invasive mechanical ventilation can be extended depending on the medical review (see DPS part 2 or Excel sheet of the medical review)
- The list of hospitalization terms (i.e.: ICU or WARD) can be extended depending on the medical review (see DPS part 2 or Excel sheet of the medical review).
- If the Subjects has no HO data, the subject is considered to be in the hospital during the trial. All other aspect of the HRS will be evaluated according to the derivation below.
- In case the readiness for discharge (RDISHOSP) is assessed more than once per day (baseline visit) we consider the worst value: in case one of the values is 'N' then the final result of that day (or baseline visit) is 'N'

Some clarification is required for following categories:

6. Death
When DM.DTHDTC<=(date of assessment)

5. Requiring invasive mechanical ventilation;
When CMSTDTC<=(date of assessment) <=CMENDTC where CMADMTP="INVASIVE MECHANICAL VENTILATION"
And CMADMDSC in ('Through Endotracheal tube' 'Through Tracheostomy tube' or 'Through ECMO')

4. Admitted to the ICU;
From the HO data set:
hostdy <=(day of assessment)<=hoendy
hoterm = 'ICU'

From the SS data set:
SSTESTCD= 'REQICU' and SSSTRESC='Y'
Or SSTESTCD= 'REASICU' and SSSTRESC='Y'
Or both REQICU and REAICU is missing and NOT (RDISHOSP = 'Y' on the day of assessment and RDISHOSP = 'Y' on the day (baseline visit) before)

OR
From the HO data set:
hostdy <=(day of assessment)<=hoendy
hoterm = 'WARD'

From the SS data set:
SSTESTCD='REASICU' and SSSTRESC='Y'
OR
SSTESTCD='REQICU' and SSSTRESC='Y'

3. Non-ICU hospitalization, requiring supplemental oxygen

Non-ICU hospitalization:

hostdy <=(day of assessment)<=hoendy
hoterm = 'Hospital inpatient Department (WARD)'
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

OR
hostdy <=(day of assessment)<=hoendy
hoterm = 'ICU'
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

OR

(day of assessment)=hoendy+1
RDISHOSP='N' on day(baseline visit) before

OR

In case re-hospitalization occurred (there is a day between the HOENDY of the previous record and HOSTDY of the next record)
(day of assessment) =HOSTDY (of the re-hospitalization)
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

AND

Requiring supplemental oxygen:

'Receiving supplemental oxygen through a face mask or nasal cannula and not being able to sustain a blood oxygen saturation of ≥94% when breathing room air for 15 minutes at any time on the day of assessment.'

FAOBJ=CHRONIC OXYGEN USE and FAORRES='N'

CMADMTP in ("Non-Invasive Mechanical Ventilation", "Nasal Cannula", "Venturi Mask", "Simple Face Mask", "Nonrebreathing Face Mask with Reservoir and One-Way Valve".)

CMTRT=SUPPLEMENTAL OXYGEN and CMSTDTC <= date of assessment <= CMENDTC

VSOXYSAT in ('N' 'NA') at any time during the day of assessment (OR is missing)

OR

'If supplemental oxygen was provided chronically pre-influenza infection (based on medical history), that amount of supplemental oxygen is exceeded to prevent hypoxia, tachypnea or dyspnea at some point on the day of assessment.'

FAOBJ=CHRONIC OXYGEN USE and FAORRES='Y'

CMARTN = 'N'

CMADMTP in ("Non-Invasive Mechanical Ventilation", "Nasal Cannula", "Venturi Mask", "Simple Face Mask", "Nonrebreathing Face Mask with Reservoir and One-Way Valve".) and CMTRT=SUPPLEMENTAL OXYGEN and CMSTDTC <= date of assessment <= CMENDTC

OR

'*Not receiving supplemental oxygen and Having a blood oxygen saturation of <94% when breathing room air for 15 minutes at any measurement on the day of assessment'*

No record in cm with oxygen supplementation

VSOXYSAT='N' at any time on the day of assessment OR [VSTESTCD='OXYSAT' and VSORRES<94% and VSOXSMRA='Y']

OR

'Not receiving supplemental oxygen and in case of known pre-influenza SpO2 <94% (eg, due to COPD), the current blood oxygen saturation on room air is lower than pre-influenza infection levels by at least 3%.'

No record in cm with oxygen supplementation

VSEVINTX= PRE-INFLUENZA INFECTION and VSTESTCD='OXYSAT and 'VSORRES<94% and VSRMAIR='Y'

VSORRES and VSTESTCD=OXYSAT (of day of assessment) < [VSORRES and VSEVINTX= PRE-INFLUENZA INFECTION and VSTESTCD='OXYSAT and VSRMAIR='Y' - 3]

2. Non-ICU hospitalization, not requiring supplemental oxygen

hostdy <=(day of assessment)<=hoendy
hoterm = 'Hospital inpatient Department (WARD)'
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

hostdy <=(day of assessment)<=hoendy
hoterm = 'ICU'
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

OR

(day of assessment)=hoendy+1
RDISHOSP='N' on day(baseline visit) before

OR

In case re-hospitalization occurred (there is a day between the HOENDY of the previous record and HOSTDY of the next record)
(day of assessment) =HOSTDY (of the re-hospitalization)
NOT (RDISHOSP='Y' on the day of assessment and RDISHOSP='Y' on day(baseline visit) before)

1. Not hospitalized

Some examples

Discharge against medical advice

If a subject is discharged 'against medical advice' on the day prior to the day of assessment, the subject will be considered as hospitalized (evaluating the others aspects of the HRS to define the correct category, e.g.: requiring supplemental oxygen, on the day of assessment)

We have a discharged against medical advice if on the day the subject is discharged (according to the HO dataset) the investigator indicated he is not ready and his SS status is discharged,

Status (HO)	Day 3 Hospitalized	Day 4 Hospitalized	Day 5 Hospitalized	Day 6 Discharged	Day 7 Home	Day 8 Home
Case 1						
ready (SS)	Not ready	Not ready	Not ready	Not ready	--	--
Status(SS)	hospitalized	hospitalized	hospitalized	Hospitalized	discharged	--
Against medical advice?					NO	
HRS	>1	>1	>1	>1	>1	HOME
Case 2						
ready (SS)	Not ready	Not ready	Not ready	Not ready	Ready	--
Status(SS)	hospitalized	hospitalized	hospitalized	Hospitalized	discharged	--
Against medical advice?					NO	
HRS	>1	>1	>1	>1	>1	HOME
Case 3						
ready (SS)	Not ready	Not ready	Not ready	Not ready	Not ready	--
Status(SS)	hospitalized	hospitalized	hospitalized	Hospitalized	discharged	--
Against medical advice?					NO	
HRS	>1	>1	>1	>1	>1	HOME
Case 4						
ready (SS)	Not ready	Not ready	Not ready	Not ready		--
Status(SS)	hospitalized	hospitalized	hospitalized	Discharged		

Against medical advice?				YES		
HRS	>1	>1	>1	>1	>1	Missing
Case 5						
ready (SS)	Not ready	Not ready	Not ready	Ready	--	--
Status(SS)	hospitalized	hospitalized	hospitalized	discharged		
Against medical advice?				NO		
HRS	>1	>1	>1	>1	HOME	HOME
Case 6						
ready (SS)	Not ready	Not ready	Not ready	Ready	--	--
Status(SS)	hospitalized	hospitalized	hospitalized	hospitalized	discharged	
Against medical advice?				NO		
HRS	>1	>1	>1	>1	HOME	HOME
Case 7						
ready (SS)	Not ready	Not ready	Ready	Ready	--	--
Status(SS)	hospitalized	hospitalized	hospitalized	hospitalized	discharged	
Against medical advice?				NO		
HRS	>1	>1	>1	HOME	HOME	HOME
Case 8						
ready (SS)	Not ready	Not ready	Not ready	--	--	--
Status(SS)	hospitalized	hospitalized	discharged	--	--	
Against medical advice?			NO			
HRS	>1	>1	>1	>1	HOME	HOME

Only in case 4 above we have a discharge against medical advice which would lead to missing values from day 8 onwards. The HRS on day 7 is defined by the other aspects of the HRS (requiring oxygen, ICU,..) on day 7 and not copied from day 6.

Requiring supplemental oxygen

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
supplemental oxygen (CM)	YES	YES	NO	NO	NO	NO
Chronic oxygen use	No	yes	Not used	Not used	Not used	Not used
returned to prior level?	Not used	N	Not used	Not used	Not used	Not used
pre influenza infection levels	Not used	Not used	Not used	Not used	Not used	93
Oxysat record < pre-influenza level at any moment during the day	Not used	Not used	Not used	Not used	Not used	yes
sustain >94% Oxy sat (VSOXYSAT)	N' missing or 'NA'	N' missing or 'NA'	N' at any time during the day	Missing or NA	YEs	Not used
Oxysat record <94% at any moment during the day	Not used	Not used	no	yes	yes	Not used
REQUIRING SUPPLEMENTAL OXYGEN?	YES	YES	YES	YES	YES	YES

To pay attention to

	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
supplemental oxygen (CM)	YES	No	No	YEs	YEs	YEs
Chronic oxygen use	No	Not used	Yes	Yes	Yes	Yes
returned to prior level?	Not used	Not used	N	Missing	N	y
pre influenza infection levels	Not used	93	Not used	Not used	Not used	Not used
Oxysat record < pre-influenza level at any moment during the day	not used	yes	Not used	Not used	Not used	Not used
sustain >94% Oxy sat (VSOXYSAT)	missing	yes	Missing	Missing	Yes	Yes
Oxysat record <94% at any moment during the day	yes	Not used	Missing	Not used	Not used	yes
REQUIRING SUPPLEMENTAL OXYGEN?	NO	YES	NO	YES	YES	NO