Janssen Research & Development

Statistical Analysis Plan

A Pilot Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Explore the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics ofJNJ-53718678 at Two Dose Levels in Non-Hospitalized Adult Subjects Infected With Respiratory Syncytial Virus

Protocol 53718678RSV2004; Phase 2a
AMENDMENT 1

JNJ-53718678

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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

Version	Effective Date	Description of Changes
1.0	18DEC2018	This is the original SAP.
2.0	27AUG2019	All changes and clarifications of planned analyses in the SAP Version 2.0 compared with the SAP Version 1.0 are listed below.

Topic or Section	Description of Changes and Clarifications of Planned Analyses
1. Introduction	The following text was added: This SAP (Version 2.0) is based on the Clinical Protocol finalized on 26 September 2018 and the Clinical Protocol Amendment INT-1 finalized on 12 April 2019. Any changes of the text in the original SAP (Version 1.0) are explicitly stated in this updated SAP.
1.4 Sample Size Justification	The statement on the RSV viral load mean change from baseline to Day 8 associated with the sample size calculation was updated without affecting the sample size itself. Using the same assumptions on the mean change and its SD, the measure of precision was updated to be the half width of the 90% confidence interval for the between-group difference in RSV viral load change from baseline, instead of the single treatment arm 90% CI. The following text: With an assumed SD of 1.85 $\log_{10}$ copies/mL, 20 subjects per treatment group will lead to a precision (90% confidence interval [CI] half width) of 0.715 and 24 subjects per treatment group to a precision of 0.647 $\log_{10}$ copies/mL for the estimate of the mean change from baseline per treatment group. was replaced by: With an assumed SD of 1.85 $\log_{10}$ copies/mL, 20 subjects per treatment group will lead to a precision (90% confidence interval [CI] half width) of 0.986 and 24 subjects per treatment group to a precision of 0.896 $\log_{10}$ copies/mL for the estimate of the difference between treatment groups in the mean change from baseline to Day 8.

2.1.2 Analysis Windows for Analysis Visits and Timepoints	1. In Table 3, the following typos were corrected for Days 10.5 and 11: Day 10.5: 231h 59 min was replaced by 233h 59 min Day 11: 232h was replaced by 234h 2. The following text was added to clarify Table 4: The secondary selection approach will only be considered in the analysis if no record is assigned to Day 3, Day 5, Day 8 and Day 14 according to the rules in the primary selection column. If 'worst per day' as per primary selection is available, same value will be assigned for the secondary selection of 'worst per day'. Otherwise, 'worst per day' as per secondary selection will be derived considering all possible values within the relative day window. The worst possible results will be selected regardless of being the closest one to target day.
2.3.2 Efficacy Analysis Set(s)	1. The following text was moved to section 5. Efficacy and further clarified: Efficacy will be analyzed on the ITT infected (ITT-i) set. The primary endpoint will also be analyzed on the Per Protocol (PP) set. 2. The following sub-section was added to ensure a minimal level of viral load at the start of treatment, allowing the antiviral effect of JNJ8678 to be evaluated: 2.3.2.2 Modified Intent-To-Treat infected (mITT-i) Set All subjects in the ITT-i analysis set with RSV viral load >= 1 $\log_{10}$ copies/mL above the Lower Limit of Quantification (LLOQ) at baseline.
3.1 Interim Analysis	As a clarification for completeness, the following text An interim analysis, encompassing efficacy, safety, and pharmacokinetics is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8. was replaced by: An interim analysis, encompassing efficacy, safety, and pharmacokinetics is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8, or

	discontinued earlier.
4.1 Demographics and Baseline Characteristics	The following baseline characteristics were added to Table 10: • Baseline RSV Viral Load (log_{10} copies/ml) by RSV Subtype • Baseline RSV Viral Load (log_{10} copies/ml) by symptom onset day
5. Efficacy	The following text was added: The primary endpoint will also be analyzed on mITT-i set and PP set.
5.1 Analysis Specifications	1. The following text was added: In addition, descriptive summaries will be presented by the randomization stratification factor, time of symptom onset (≤3 days vs >3 days before randomization). 2. The following clarification was added: For all the stratified statistical analyses, the derived randomization stratification factor will be used instead of the randomization stratification factor as collected in the IWRS.
5.2.1 Definitions	1. As the protocol was updated (Protocol-Amendment 1 dated on 12 April 2019) to include Day 5 as an additional timepoint for the assessment of the area under the RSV viral load-time curve (AUC), the following text was removed: Change from planned analyses; For viral load the AUC for Day 5 has been included. 2. The following text was added as a clarification on the calculation of the viral load of AUC with missing data: Carrying forward should only be performed if the time between the available observation and the value at xxh is at most 24 hours. In case the last observation is before xxh, and the value at xxh cannot be determined, the AUCs through xxh and through any later timepoint will not be derived.
5.2.2 Analysis Methods	1. A clarification about the subgroup analyses for AUC viral load was added: The homogeneity of treatment effect on the occurrence of AUC viral load from baseline to Days 3, 5, and 8 across subgroups

	will be examined using the same MMRM model approach for the primary analysis, but also includes the subgroup-by-treatment and subgroup-by-visit interaction terms in the model. A forest plot will present the Least Square means and 95% CI for all subgroups of interest. 2.A clarification about the stratified Cox proportional hazard model as well as the calculation of the 90% confidence intervals based on the Kaplan-Meier method was added: Time-to event variable will be analyzed and plotted using Kaplan-Meier estimates analysis. The estimate of the hazard ratio (HR) and the 90% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (derived randomization stratification factor: ≤3 days, >3 days) and including treatment group as a covariate. 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 90% confidence intervals based on the Kaplan-Meier method, will be presented by treatment group. 3.A clarification about the subgroup analyses for the time to virus undetectable was added: The potential impact of selected variables that identify the subgroups of interest on the time to virus undetectable will be assessed by the stratified Cox proportional hazard model. The model will be stratified by the randomization stratification factors and include treatment group and subgroup variable as covariates, and the subgroup-by-treatment interaction term. A forest plot will present the HRs and 90% CI for all subgroups of interest. 4. A clarification about the calculation of the difference in proportion of subjects with undetectable RSV viral load was added. The subjects with detectable or quantifiable RSV viral load are grouped into one category, so the subjects can be classified as either with RSV viral load 'undetectable' or 'detectable or quantifiable': The difference in proportions for undetectable versus detectable/quantifiable between each active group and placebo, will be tabulated descriptively (n and % per treatment group), for

	each post baseline timepoint.
5.3. Secondary Endpoints - Clinical Course	According to Protocol-Amendment 1, the RI-PRO (for newly recruited subjects) was replaced by RiiQ (RI-PRO still being collected at certain timepoints). Therefore, endpoints derived from RiiQ were added: • Duration and severity of signs and symptoms of RSV infection assessed through either the Respiratory Infection Patient Reported Outcome (RI-PRO) or the Respiratory Infection Intensity and Impact Questionnaire [RiiQ] questionnaire, and Additional Questions about Health and Functioning. • Time to resolution of selected RSV symptoms as reported by the subject through either the RI-PRO or RiiQ.
5.3.1.1 ePROs	According to Protocol-Amendment 1, the RI-PRO (for newly recruited subjects) was replaced by RiiQ (RI-PRO still being collected at certain timepoints). Therefore, information regarding the RiiQ, calculation and analyses of the RiiQ (symptom or impact) domain scores, RiiQ key symptom score, and related time to (complete) resolution were added to this section. In addition, details about the RI-PRO key RSV symptom score and related time to (complete) resolution analyses were added. Time to (complete) resolution analyses based on the common key symptoms from either RI-PRO or RiiQ were also added to this section.
5.3.2.1 Endpoint-specific analysis methods	1. According to Protocol-Amendment 1, the RI-PRO (for newly recruited subjects) was replaced by RiiQ (RI-PRO still being collected at certain timepoints). Therefore, the following text was added: Changes from baseline on each of the RI-PRO and RiiQ domains will be analyzed using a restricted maximum likelihood based repeated measures approach as per Section 5.2.2. An unstructured covariance structure will be selected. 2. The typo regarding the confidence level for the confidence interval based on Wilson score test was corrected: '95% confidence interval' was replaced by '90% confidence interval': The difference in proportions between each active group and

	placebo will be tabulated, and summaries will include 2-sided 90% confidence intervals based on the Wilson score test. 3. The following text was added under 'Time to resolution of symptoms, Time to return to usual health and Time to return to usual activity': The estimate of the hazard ratio (HR) and the 90% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (derived randomization stratification factor: ≤3 days, >3 days) and including treatment group as a covariate. 4. A clarification about the calculation of the 90% confidence intervals was added under 'Time to resolution of symptoms, Time to return to usual health and Time to return to usual activity': A summary table including number of subjects included in the analysis, number of subjects censored, 25^{th} and 75^{th} percentiles and median time-to event, with 90% confidence intervals based on the Kaplan-Meier method, will be presented by treatment group. 5. A clarification on the subgroup analyses for the time to resolution of symptoms was added: The potential impact of selected variables that identify the subgroups of interest on the time to resolution of symptoms will be assessed by the stratified Cox proportional hazard model. The model will be stratified by the randomization stratification factors and include treatment group and subgroup variable as covariates, and the subgroup by treatment interaction term. A forest plot will present the HRs and 90% CI for all subgroups of interest.
5.4. Sensitivity Analyses	The following sensitivity analyses were added: Sensitivity analyses to assess the robustness of the primary efficacy analysis of viral load AUC will be performed by including the stratification factor, RSV symptom onset (≤3 days or > 3 days) as collected in the IWRS, in the mixed-effects model. Additionally, the primary efficacy analysis will be repeated on the mITT-I set. For the time to resolution of selected RSV symptoms, sensitivity

	analyses will be performed considering 4 different imputation methods: • Method 1: from first resolution (score 0 or 1) after last unresolved value onwards, impute missing data as resolution. • Method 2: impute all missing values as unresolved (score >1). • Method 3: impute all missing values in-between resolved observations (score 0 or 1) as resolved. • Method 4: impute all missing values as unresolved (score >1), except when in-between resolved values where resolved is imputed.
5.6 Exploratory Analyses	According to Protocol-Amendment 1, the RI-PRO (for newly recruited subjects) was replaced by RiiQ (RI-PRO still being collected at certain timepoints). Therefore, information regarding the RiiQ analyses was added under the 'Clinical course endpoints'.
7.2. Analysis Methods	A clarification about the method used in calculating the 90% confidence interval for a binomial proportion was added as follows: The proportion of subjects requiring any medical encounter will be shown in a frequency tabulation by treatment group with the corresponding 90% confidence interval (exact Clopper-Pearson method).
8.1 Definitions	1. Position 127 was added to the following text: Long list of 20 F-gene positions of interest for the class of RSV fusion inhibitors, based on in vitro selection experiments, clinical observations, and/or in vitro reduced susceptibility to RSV fusion inhibitors: positions 127, 138, 140, 141, 143, 144, 323, 338, 392, 394, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517. 2. The following clarification was added for the 'Last Evaluable On-Treatment Time Point', under 'Analysis Time Points': In case no On-Treatment assessment is available, the first assessment during Follow-Up is selected instead. 3. 'During the follow-up phase' was added as a clarification to the definition of the 'Time Point of Sequence during the Follow-Up phase', under 'Analysis Time Points'.

ABBREVIATIONS

AE	adverse event
AFT	Accelerated Failure Time
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DMID	Division of Microbiology and Infectious Diseases
DRC	Data Review Committee
DPS	Data Presentation Specifications
ECG	Electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
HCP	Health Care Provider
HRQOL	Health-Related Quality of Life
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IQ	Interquartile
ITT-i	Intent-to-Treat infected
IRBs	Institutional Review Boards
IWRS	interactive web response system
LLOQ	Lower limit of quantification
LOCF	last observation carried forward
LOD	Limit of detection
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT-i	Modified Intent-to-Treat infected
PD	Pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
PRO	Patient Reported Outcome
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RI-PRO	Respiratory Infection-Patient Reported Outcomes questionnaire
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SpO_2	peripheral capillary oxygen saturation
TD	Target Detected
TND	Target Not Detected
TEAE	treatment-emergent adverse event

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the efficacy and safety analyses of the study JNJ-57318678RSV2004. The SAP is to be interpreted in conjunction with the protocol.

This SAP (Version 2.0) is based on the Clinical Protocol finalized on 26 September 2018 and the Clinical Protocol Amendment INT-1 finalized on 12 April 2019. Any changes from the text in the original SAP (Version 1.0) are explicitly stated in this updated SAP.

A detailed analysis plan for the pharmacokinetic and pharmacokinetic/pharmacodynamics data will be described in a Clinical Pharmacology Analysis Plan (CPAP).

JNJ-53718678 is an investigational RSV specific fusion inhibitor belonging to the indole chemical class and is under development for the treatment of RSV infection. The study drug shows in vitro activity against a panel of viruses belonging to both the RSV subfamilies A or B. In addition, antiviral activity of JNJ-53718678 was demonstrated during clinical studies in healthy adults inoculated with RSV (study 53718678RSV2001) and in pediatric subjects hospitalized due to RSV-infection (study 53718678RSV1005).

1.1. Trial Objectives

Primary Objective

The primary objective of the study is to explore the antiviral effect of JNJ-53718678 at 2 dose levels (80 mg and 500 mg) once daily for 7 days in adults with RSV infection, as measured by RSV viral load in nasal secretions by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay.

Secondary Objectives

The secondary objectives are to explore in adults with RSV infection, after repeated oral dosing with JNJ-53718678:

- The safety and tolerability of JNJ-53718678
- The impact of JNJ-53718678 on the clinical course of RSV infection
- The pharmacokinetics of JNJ-53718678.

Exploratory Objectives

The exploratory objectives are to explore in adults with RSV infection after repeated oral dosing with JNJ-53718678:

- The relationship between antiviral activity and clinical course
- The relationship between pharmacokinetics and pharmacodynamics (selected antiviral activity
- parameters, clinical outcomes, and safety parameters)

- Potential differences in antiviral activity and clinical course between:
    - otherwise healthy and comorbid subjects;
    - subjects with symptom onset ≤3 days before randomization and subjects with symptom onset >3 days before randomization.
- The occurrence of complications associated with RSV per investigator assessment after initiation of treatment
- Medical resource utilization, including hospitalization, for clinical management of subjects during treatment and posttreatment follow-up
- The impact of the baseline RSV viral subtype and genotype on the antiviral activity and clinical course
- The emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678
- The RSV infectious virus titers as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay)
- Impact of RSV and its treatment on health-related quality of life (HRQOL).

1.2. Trial Design

This is a Phase 2a, randomized, double-blind, placebo-controlled study to explore the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics of JNJ-53718678 at 2 dose levels (80 mg and 500 mg) once daily for 7 days in adult subjects with respiratory illness due to RSV infection. Subjects may be otherwise healthy or comorbid and should not be in need of hospitalization.

A population of 75 subjects is targeted. However, given the recruitment challenges associated with the seasonality of RSV, a minimum of 63 subjects may be considered sufficient to complete the study.

The study includes a Screening Period (Day -1 to Day 1), a Treatment Period (Day 1 to Day 8), and a Follow-up Period (Day 9 to Day 28[±3]). The total study duration for each subject is 29 days (screening included).

After screening, eligible subjects are randomized on Day 1 (1:1:1) to receive 1 of 3 treatments:

- Treatment A: 500 mg JNJ-53718678 once daily for 7 days (n = 25 [target]);
- Treatment B: 80 mg JNJ-53718678 once daily for 7 days (n = 25 [target]);
- Treatment C: placebo once daily for 7 days (n = 25 [target]).

Randomization is stratified by time of symptom onset (≤3 days vs >3 days before randomization). Subjects with symptom onset >3 days before randomization may account for maximum of 50% of all enrolled subjects.

An interim analysis is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8.

A Data Review Committee (DRC) is in place for this study. The DRC monitors safety data during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring.

1.3. Statistical Hypotheses for Trial Objectives

The primary objective of the study is to explore the antiviral effect of JNJ-53718678 at 2 dose levels (80 mg and 500 mg) once daily for 7 days in adults with RSV infection, as measured by RSV viral load in nasal secretions by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay.

No statistical hypotheses are to be tested.

1.4. Sample Size Justification

The interim results (estimates of mean AUC and change from baseline of RSV viral load ±SD) of study 53718678RSV1005 were the basis of the sample size calculation. In that study, median (range) time to onset of symptoms was 5 (2-12) days and baseline viral load was 5.3 (2.1-8.3) log10 copies/mL.

For the AUC viral load from Day 1 to Day 7, a (placebo) point estimate of 490 and an SD of 135 log10 copies x hr/mL was observed for the AUC viral load from Day 1 to Day 7. The sample size was determined in order to obtain estimates of the mean AUC viral load with a precision of approximately 50 log10 copies x hr/mL of the true value with 90% confidence; with 20 subjects per treatment group the half-width of the 90% confidence would be approximately 52 and with 24 subjects per treatment group the precision would be approximately 47 log10 copies x hr/mL.

For the change from baseline (on Day 2 or Day 3), (placebo) point estimates of -0.11 and -0.33 and SDs of 1.85 and 1.56 log10 copies/mL, respectively, were observed. The observed difference (active versus placebo) was -1 to -2 log10 copies/mL. With an assumed SD of 1.85 log10 copies/mL, 20 subjects per treatment group will lead to a precision (90% confidence interval [CI] half width) of 0.986 and 24 subjects per treatment group to a precision of 0.896 log10 copies/mL for the estimate of the difference between treatment groups in the mean change from baseline.

As further guidance for the design, the power to detect a dose-response was calculated. To evaluate a potential dose-response, 3 contrasts will be tested: a contrast with no difference between the 2 active doses tested against placebo; a contrast with no difference between low dose and placebo tested against high dose; and a contrast with a linear dose-response relationship with respect to the active doses. No correction for multiplicity is considered in view of the exploratory nature of the study. Based on 10,000 simulations, and assuming a reduction in AUC viral load of 20% of high dose versus placebo, the power to detect a positive dose-response relationship will be between 79% and 86% (depending on the effect of the low dose) with a total sample size of 60, and between 83% and 89% with a total sample size of 72.

To account for potential false-positive RSV screening testing (ie, diagnosed with RSV infection using a rapid PCR-based or rapid antigen-detection test, but negative at the central lab using a qRT-PCR assay, and therefore not included in the primary analysis population of ITT-i) and withdrawals from treatment for abnormal screening laboratory results, an overage of approximately 5% will be enrolled, ie, 75 subjects are targeted.

In view of the seasonality of the disease, recruitment will be halted if at the end of a hemispheric RSV season 63 or more subjects have been enrolled and dosed. If at the end of a hemispheric RSV season the minimum of 63 dosed subjects is not reached, recruitment will continue in a next RSV season until this minimum has been reached, up to a maximum of 75 subjects to be enrolled overall.

1.5. Randomization and Blinding

Central randomization is implemented in this study. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject. Subjects are randomly assigned to 1 of the 3 treatments to receive either a high (500 mg/day) or a low (80mg/day) dose of JNJ53718678 or placebo in 1:1:1 ratio. The randomization is balanced by using randomly permuted blocks and stratified by time since symptom onsent at randomization (≤3 days vs >3 days). Subjects with symptom onset >3 days before randomization may account for maximum of 50% of all enrolled subjects.

In order to maintain study blind, all subjects receive once daily the same total volume of study drug solution divided over 2 separate but sequential intakes at the same time of day.

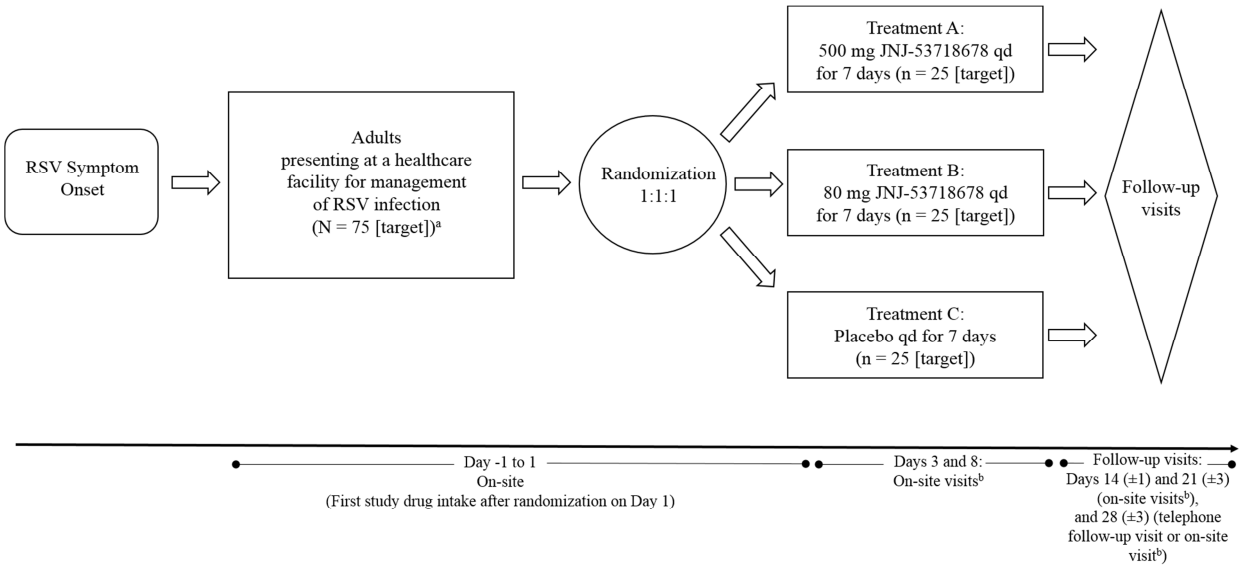
2. GENERAL ANALYSIS DEFINITIONS

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

2.1. Phase Definitions, Visit Windows and Baseline

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



2.1.1. Phase Definitions

Phases will be defined as in Table 1.

Table 1: Definition of Analysis Phases

Analysis Phase [Phase No.]	Start Date/Time	End Date/Time
Screening [1]	00:00 of the date of signing the informed consent form	1 minute before the first study drug administration in the trial
Treatment [2]	Date and time of first study drug administration in the trial (Study Day 1)	23:59 of the last day of treatment +3 days (or date of last contact if still on treatment) or 23:59 of the cut-off date for the IA, whichever occurs first
Follow-up [3]	1 minute after End of Treatment Phase	23:59 of the day of trial termination (date of last contact) or 23:59 of the cut-off date for the IA, whichever comes first

Assessments will be assigned to phases based on their datetime, but seconds will be ignored overall. If the day part of the start date of the assessment is present but the time part is missing, the assessment will be treated as if it started at 00:00 on the day of the event (unless for Adverse Events see details in Section 2.5). If the day part of the end date of the assessment is present but the time part is missing, the assessment will be treated as if it happened at 23:59 on the day of the assessment. No formal imputation will be done, these rules will only be applied to allocate assessments to phases.

2.1.2. Analysis Windows for Analysis Visits and Timepoints

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (please see Table 2, Table 3 and Table 4) are the visit windows and the target days for each visit defined in the protocol.

For the analyses of measurements scheduled once daily the following rules will be applied to have only one evaluation per subject per analysis visit:

- If two assessments fall within the same visit window, the measurement closest to the target day will be used.
- If the assessments are equidistant, the last measurement within the interval will be used.
- If there are two measurements on the same date and time, then the measurement with the highest sequence number will be used.

Once baseline is assigned, any assessment performed prior to the defined baseline, will be assigned to Screening. Screening visits will not be used in summary tables but only in listings.

Any assessment performed within Day 1 but after first drug intake, will be assigned to Day 1 post-dose.

Exceptions to the general rule:

- *Viral Load*

  For the analyses of viral load (scheduled once daily), if multiple nasal swabs were taken on a single day, the above rules will only be applied after having determined per day the maximum viral load. The maximum viral load on a day will be used for windowing. Please notice that baseline viral load follows the rules described in Section 2.1.4.

- *Electrocardiogram*

  In case there is more than one assessment per analysis visit window, the following rule will be used to have only one evaluation per analysis timepoint:

  – The average of the last available complete ECG triplicate should be considered in first instance.

  – In absence of complete triplicate ECGs, the average of the last available ECG duplicate should be considered.

  – In absence of complete or partial triplicates, the last available single ECG can be used.

If an assessment is performed but not planned per protocol, it may be assigned to a visit window for consistency, based on the relative day. However, it will not be shown in the summary tables and figures as only scheduled visits per protocol are used.

Screening visits will not be used in summary tables but only in listings. All information will be listed.

Table 2: Visit Windows

Analysis Visit [scheduled Analysis Visit No.]	TIME INTERVAL (Day)* [TARGET TIMEPOINT (Day)]						
	EQ-5D-5L[$]	**Clinical Parameters (excluding Body Temp.)**	**Body Temp.**	**Viral Load**	**Vital Signs**	**ECG / PK**	**Clinical Laboratory**
Screening [-1]	<1 [-1 to 1]	<1 [-1 to 1]	<1 [-1 to 1]	<1 [-1 to 1]	<1 [-1 to 1]	<1 [-1 to 1]	<1 [-1 to 1]
Baseline+ [0]	<=1 [1]	<=1 [1]	<=1 [1]	<=1 [1]	<=1 [1]	<=1 [1]	<=1 [1]
Day 1 [1]	1 [1]		1 [1]	1 [1]			
Day 2 [2]	2 [2]		2 [2]	2 [2]			
Day 3** [3]	2 to 5 [3]	2 to 5 [3]	3 [3]	3 [3]	2 to 5 [3]	2 to 5 [3]	2 to 5 [3]
Day 4 [4]	4 [4]		4 [4]	4 [4]			
Day 5 [5]	5 [5]		5 [5]	5 [5]			
Day 6 [6]	6 [6]		6 [6]	6 [6]			
Day 7 [7]	7 [7]		7 [7]	7 [7]			
Day 8** [8]	8 [8]	6 to 10 [8]	8 [8]	8 [8]	6 to 10 [8]	6 to 10 [8]	6 to 10 [8]
Day 9*** [9]	9 [9]		9~ [9]	9 [9]			
Day 10*** [10]	10 [10]		10 [10]	10 [10]			
Day 11*** [11]	11 [11]		11 [11]	11 [11]			
Day 12*** [12]	12 [12]		12 [12]	12 [12]			
Day 13*** [13]	13 [13]		13 [13]	13 [13]			
Day 14** [14]	14 [14]	11-17 [14]	13 to 17 [14]	13 to 17 [14]	11 to 17 [14]	11 to 17 [14]	11 to 17 [14]
Day 15 [15]	15 [15]						
Day 16 [16]	16 [16]						
Day 17 [17]	17 [17]						
Day 18 [18]	18 [18]						
Day 19 [19]	19 [19]						
Day 20 [20]	20 [20]						

Table 2: Visit Windows

Day 21** [21]	21-24 [21]	18-24 [21]	18-24 [21]	18-24 [21]	18-24 [21]	18-24 [21]	18-24 [21]
Day 28 [28]	25 to +∞ [28]	25 to +∞ [28]	25 to +∞ [28]	25 to +∞ [28]	25 to +∞ [28]	25 to +∞ [28]	25 to +∞ ## [28]

+ Baseline is defined as the last measurement before first study drug intake. Please also see section 2.1.4

* Relative to [Study Day 1]; ** on site visits *** only if symptomatic; ## only for hematology and biochemistry if needed

$ visit windows to be applied as well to RI-PRO, Additional Questions about Health and Functioning when QD scheduled is applicable (from Day 14- 312h and onwards) or if treatment discontinued prematurely but follow up visits are performed; If time of assessment between 00:00 to 01:59, it will be considered as if performed within the previous day. For RI-PRO and Additional Questions about Health and Functioning BID please see also Table 3, Table 4 and Table 5.

Respiratory Infection Patient Reported Outcomes (RI-PRO), Respiratory Infection Intensity and Impact Questionnaire (RiiQ), and Additional Questions about Health and Functioning are collected twice daily (BID) from Day 1 through Day 13. Windows for these assessments are defined relative to the first study drug intake (0h): 12h (+/-6h), 24h (+/-6h), 36h (+/-6h), etc.

Table 3: Visit Windows for ePRO

Analysis time	time* Interval	Target Time
12h (Day 1.5*)	>0h$; 17h59min	12h
24h (Day 2.0)	18h; 29h 59 min	24h
36h (Day 2.5)	30h; 41h 59min	36h
48h (Day 3.0)	42h; 53h 59min	48h
60h (Day 3.5)	54h; 65h 59min	60h
72h (Day 4.0)	66h; 77h 59min	72h
84h (Day 4.5)	78h; 89h 59min	84h
96h (Day 5.0)	90h; 101h 59min	96h
108h (Day 5.5)	102h; 113h 59min	108h
120h (Day 6.0)	114h; 125h 59min	120h
132h (Day 6.5)	126h; 137h 59min	132h
144h (Day 7.0)	138h; 149h 59min	144h
156h (Day 7.5)	150h – 161h 59min	156h
168h (Day 8.0)	162h; 173h 59min	168h
180h (Day 8.5)	174h; 185h 59min	180h
192h (Day 9.0)	186h; 197h 59min	192h
204h (Day 9.5)	198h; 209h 59min	204h
216h (Day 10.0)	210h; 221h 59min	216h
228h (Day 10.5)	222h; 233h 59 min	228h
240h (Day 11.0)	234h; 245h 59min	240h
252h (Day 11.5)	246h; 257h 59min	252h
264h (Day 12.0)	258h; 269h 59min	264h
276h (Day 12.5)	270h; 281h 59min	276h
288h (Day 13.0)	282h; 293h 59 min	288h
300h (Day 13.5)	294h; 305h 59min	300h
312h (Day 14.0)	306h; 317h 59min	312h

*from first drug intake time; $ post baseline;

For analyses for which we need at most one assessment per day (e.g.: where BID assessments but daily assessment to be used in the analysis) we take the worst over 24 hours according to Table 4.

Table 4: Worst per Day

Analysis time	Primary Selection	Secondary Selection TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)]
Baseline		
Day 2	Worst [12h; 24h]	
Day 3	Worst [36h; 48h]	3 [3]
Day 4	Worst [60h; 72h]	
Day 5	Worst [84h; 96h]	4-6 [5]
Day 6	Worst [108h; 120h]	
Day 7	Worst [132h; 144h]	
Day 8	Worst [156h; 168h]	8-9 [8]
Day 9	Worst [180h; 192h]	
Day 10	Worst [204h; 216h]	
Day 11	Worst [228h; 240h]	
Day 12	Worst [252h; 264h]	
Day 13	Worst [276h; 288h]	
Day 14	Worst [300h; 312h]	13-15 [14]

The secondary selection approach will only be considered in the analysis if no record is assigned to Day 3, Day 5, Day 8 and Day 14 according to the rules in the primary selection column. If 'worst per day' as per primary selection is available, same value will be assigned for the secondary selection of 'worst per day'. Otherwise, 'worst per day' as per secondary selection will be derived considering all possible values within the relative day window. The worst possible results will be selected regardless of being the closest one to target day.

Additionally, each BID assessment is defined as a morning or evening assessment based on the timing of the assessment as defined in Table 5.

Table 5: ePRO Time Slot in a Day

Slot of the Day	Time
Morning	02:00 am – 13:59 pm
Evening	14:00 – 01:59 am*

*from 00:00 to 01:59 to be considered as if performed within the previous day.

2.1.3. Study Day and Relative Day

Study Day 1 is defined as the date of first study medication intake (reference day). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

For visits on or after the reference day (Day 1) the relative day for a visit is defined as:

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

and for visits before the reference day (Day 1)

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

There is no 'Day 0'.

2.1.4. Baseline

In general, the baseline record is defined as the last record before the first intake of the study drug except for the following assessments where additional rules will be applied:

- RSV RNA viral load:
  - Last available assessment within the 24h prior to or at the same time of first drug intake will be considered as baseline.
  - If no assessment within the 24h prior to or at the same time of first drug intake, but there is a result available no later than 1h post first study drug intake, the baseline assessment will be the first assessment completed within 1h post first drug intake.
  - If none of the above assessments are available, but there is an assessment available before the 24h prior to first drug intake, it will be considered as baseline.
- ePRO:
  - Last available assessment within the 8h prior to first drug intake.
  - if no assessment is available within 8 hours prior to first drug intake, but there is an assessment completed within 1-hour post first intake, then baseline assessment will be the assessment completed within 1-hour post first intake.
  - If none of the above assessments are available, but there is an assessment available before the 8h prior to first drug intake, it will be considered as baseline.

If no record available at all before first drug intake, baseline will be considered as missing.

2.2. Pooling Algorithm for Analysis Centers

Since it is expected that for this trial subjects will be recruited over a large number of centers with a small number of subjects per study center, there is no need to check for treatment by center interactions. In addition, the primary endpoint is an objective endpoint, which is evaluated by a central assay, no heterogeneity across centers is anticipated. Therefore, there is no need for a pooling algorithm for analysis centers.

2.3. Analysis Sets

2.3.1. All Randomized Analysis Sets

2.3.1.1. All Randomized Analysis (RAND) Set

All randomized subjects with a randomization date regardless of being treated or not.

2.3.2. Efficacy Analysis Set(s)

2.3.2.1. Intent-To-Treat infected (ITT-i) Set

All randomly assigned subjects who received at least 1 dose of study drug and who have an RSV infection confirmed by a PCR-based assay at the central laboratory at baseline (records up to 1 hour after first medication intake can be used in case no pre-treatment observation is available). Subjects in the ITT-i set will be analyzed according to the treatment they were randomly assigned to.

The ITT-i set definition applies also to the interim analysis. However, if a subject has no central lab confirming the RSV infection at baseline, that subject will not be included in the ITT-i set for the interim analysis purpose.

2.3.2.2. Modified Intent-To-Treat infected (mITT-i) Set

All subjects in the ITT-i analysis set with RSV viral load ≥ 1 $\log_{10}$ copies/mL above the Lower Limit of Quantification (LLOQ) at baseline.

2.3.2.3. Per Protocol Analysis (PP) Set

All subjects in the ITT-i analysis set with the exclusion of any subjects deemed to have a major protocol deviation that may affect the assessment of efficacy. Such major protocol deviations will be identified, revised and documented prior to database lock based on the following criteria:

- Entered but did not satisfy criteria, violation of:
  - inclusion criteria 4 or 5,

    AND/OR
  - exclusion criteria 1, 4, 7, 8, 9,14 or 16

Please see Section 4.1 and 4.2 of the protocol for full description of the criteria.

- Received wrong treatment or incorrect dose
  - The actual treatment not the same as the planned treatment
  - Subjects missed more than 1 dose.

- Other:
  - Unplanned unblinding has taken place during the study.

  - Insufficient post-baseline viral load samples collected (should have at least baseline and 2 post-dose samples between Day 2 and Day 5).

- Received concomitant treatment that may affect the efficacy of the trial medication.

Complete list of concomitant medications to be considered for major protocol violation will be finalized before the database lock.

Note that in the PP set, subjects will be treated as randomized (by definition). Analyses on the PP set will only be performed if >10% subjects in the ITT-i set are excluded from the PP set.

2.3.3. Safety Analysis Set

2.3.3.1. Safety Analysis Set (SAF)

The safety analysis set includes all subjects who received at least 1 dose of study agent, analyzed as treated.

The actual treatment is determined as the treatment for which the majority of drug dose is taken.

The Safety set will be used to perform the evaluation of all safety variables and will be used for listings.

2.4. Definition of Subgroups

The following subgroups will be investigated for efficacy, including the primary endpoint (viral load) and key clinical course endpoints (duration and severity of sign and symptoms, time to resolution of RSV symptoms and respiratory rate, heart rate, body temperature and peripheral capillary oxygen saturation (SpO_2). For safety, subgroup analyses will be limited to age group and presence of any comorbid disease associated with risk factors for severe RSV disease.

Table 6: Subgroups

Subgroup	Definition
Symptom Onset	• Subjects with symptom onset ≤3 days before randomization • Subjects with symptom onset >3 days before randomization
Baseline RSV Viral Subtype	• RSV A • RSV B • RSV A+B
Age	• <65 years and >=65
Baseline Viral Load	Central Viral Load (VL) • VL≥1 log10 copies/mL above the LLOQ at baseline • otherwise
Presence of any Comorbidities	• No • Yes
Presence of any comorbid disease associated with risk for severe RSV disease	• No • Yes

Table 6: Subgroups

Subgroup	Definition
Comorbid diseases associated with risk for severe RSV disease	• Asthma [Yes/No] • COPD [Yes/No] • CHF [Yes/No] • CAD (coronary artery disease) [Yes/No]
Other conditions/therapy of potential interest due to risk of infections in general	• Diabetes mellitus [Yes/No] • CRF (Chronic Renal Failure) [Yes/No] • Use of systemic corticosteroids prior to or during the treatment phase [Yes/No],
Prior use of systemic corticosteroids Note: use in the 7 days prior to randomization and not continued after first dose	• No • Yes
Co-infection Note: based on respiratory pathogens panel assay performed at baseline	• No • Yes

Subgroup analyses will be performed for efficacy primary endpoint and key clinical course endpoints in case at least 15 subjects are enrolled in any of the subgroup categories.

Medical review will be done immediately before database lock on a list with unique coded medical history terms (MedDRA Preferred Terms) to indicate which subjects had comorbidities.

2.5. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows in derivations, but original information should remain in the database:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of first dosing of the study medication.
  - The day of first dosing of the study medication, if the month/year of the onset of AE is the same as month/year of the first dosing of the study medication and month/year of the AE resolution date is different.
  - The day of first dosing of the study medication or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dosing of the study medication and month/year of the AE resolution date are same.
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first dosing of the study medication.

- Month and day of the first dosing of the study medication, if this date is the same year that the AE occurred.
- Last day of the year if the year of the AE onset is prior to the year of the first dosing of the study medication.
- The AE resolution date.

Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE

3.1. Interim Analysis

An interim analysis, encompassing efficacy, safety, and pharmacokinetics is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8, or discontinued earlier. Enrollment will not be paused during the interim analysis.

From the subgroup analyses planned for the final analysis, the following will be included for the interim analysis irrespective of the number of subjects within the subgroup:

- Efficacy analysis: Symptoms onset day
- Safety analysis: age group and presence of any comorbid disease associated with risk factors for severe RSV disease.

Exploratory endpoints will not be included in the interim analysis except for an evaluation of the possible effect of the time since onset of symptoms on antiviral activity and clinical course.

Additional interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities. The primary (final) analysis will be performed after the last subject has completed his/her last visit of the study. Since this is an exploratory, hypothesis-generating study, no adjustments for multiplicity will be performed.

3.2. Data Review Committee

A Data Review Committee (DRC), comprised of senior sponsor personnel outside of the central sponsor team and not involved in study conduct, will be established. The DRC will monitor

safety data during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring.

The central sponsor team, composed by clinical leader, statistician(s), virologist, PK leader, pharmacometrician and statistical programmers will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study. The DRC will decide on the implementation of the recommendations based on the review of the interim results of the study.

Further details of the DRC, eg, composition and activities, are described in the DRC charter.

4. SUBJECT INFORMATION

All subject information analyses will be done on the ITT-i Set and the Safety Set, unless specified otherwise for a specific display (in the DPS).

4.1. Demographics and Baseline Characteristics

Table 7 presents a list of the demographic variables that will be summarized by treatment group and overall.

Table 7: Demographic Variables

	Summary Type
Continuous Variables:	
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight at baseline (kg)	
Height at baseline (cm)	
Body Mass Index[b] at baseline (BMI) (kg/m^2) = weight (kg)/(height (m))²	
Categorical Variables	
Age (<65 years and >=65)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Country	

a: If multiple race categories are indicated, the Race is recorded as 'Multiple'. The specifications of the categories 'Other' and 'Multiple' will only be listed.

b: Rounded to 1 decimal. Even if available in the raw data, BMI will be calculated from baseline weight and height.

Symptom Onset at Randomization will be calculated by considering:

- Symptom onset start date and time slot of the day
- Randomization date and time slot of the day

as indicated in Table 8.

Table 8: Time Slot in a Day

Slot of the Day	Time
Night	00:00 midnight – 05:59 am
Morning	06:00 am – 11:59 noon
Afternoon	12:00 noon – 17:59 (or 5:59 pm)
Evening	18:00 – 23:59

symptom onset days = randomization date – reported symptom onset date + correction factor for time of the day

The correction factor is:

- 0: in case time slot on day of randomization ≤ time slot on day of symptoms
- 1: in case time slot on day of randomization > time slot on day of symptoms

Table 9: Correction Factor for Time Slot in a Day

	Randomization Day			
Symptom Onset Day	Night	Morning	Afternoon	Evening
Night	0	1	1	1
Morning	0	0	1	1
Afternoon	0	0	0	1
Evening	0	0	0	0

In case the time slot of the day of symptom onset is missing, no correction factor will be applied.

Similar definition will be used to calculate time for symptom onset at first treatment.

Table 10 presents a list of the baseline characteristics that will be summarized by treatment group and overall. Baseline characteristics will also be summarized by presence of comorbidities (yes, no) and by symptom onset (≤3 days, >3 days).

Table 10: Baseline Characteristics

	Summary Type
Continuous Variables:	
Duration of RSV symptoms prior to randomization (days)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Duration of RSV symptoms prior to first treatment (days)	
Baseline RSV Viral Load (log_{10} copies/ml)	
Baseline RSV Viral Load (log_{10} copies/ml) by RSV Subtype	
Baseline RSV Viral Load (log_{10} copies/ml) by symptom onset day	
Respiratory Rate (breaths/min)	
Heart Rate (beats/min)	
Oxygen Saturation (%)	
Categorical Variables	
Baseline RSV Subtype (RSV A, RSV B, RSV A+B)	Frequency distribution with the
Symptom Onset (≤3 days, >3 days)	
Co-infection (no, yes)	
Presence of ANY Comorbidities (no, yes)	
Comorbid disease associated with risk for severe RSV disease (no, yes)	
Each of the following diseases (subcategories of the above): - Asthma - COPD	

Table 10: Baseline Characteristics

	Summary Type
- CHF - CAD	number and percentage of subjects in each category.
Other conditions/therapy of potential interest due to risk of infections in general (yes, no)	
Each of the following conditions/therapies (subcategories of the above): - diabetes mellitus - CRF - use of systemic corticosteroids prior to or during the treatment	
History of wheezing associated with acute respiratory infection? (no, yes)	
Contact with HCP before presenting (no, yes)	
If Yes, specify the type of HCP (General Practitioner, Other)	
History of Tobacco use (current, former, never)	

4.2. Disposition Information

Summaries will be provided for the following disposition information:

- Number of screen failures, randomized (RAND), randomized and not treated, not randomized and treated, safety set (SAF), ITT-i set and PP set (PPS).
- Number of subjects who completed or discontinued treatment and the study, with a breakdown of the reason of discontinuation.
- Number of subjects per phase and per visit in the trial.

4.3. Treatment Compliance

Study treatment compliance will be listed as well as the reasons for non-dispensing assigned drug, or for adjusting the dose.

4.4. Extent of Exposure

Extent of exposure (days) is defined as (date of the last dose of study treatment – date of the first dose of study treatment) +1.

Note: treatment interruptions will not be taken into account.

Extent of exposure will be summarized descriptively by treatment group.

4.5. Protocol Deviations

Only major protocol deviations will be defined in this trial. All major protocol deviations (please see Section 2.3.2.3 for details) will be tabulated and listed. Those that may affect the assessment of efficacy will be documented prior to database lock.

4.6. Medical History

The medical history records will be listed; separate listings will be provided for comorbid diseases associated with RSV.

4.7. Prior and Concomitant Medications

Medications taken from the date the ICF is signed through to the end of study will be summarized by preferred term using the World Health Organization-Drug Dictionary 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.)

The part on concomitant medication will be shown by ATC class level up to level 3.

If a prior/concomitant therapy record missed 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/concomitant using the available partial information, without imputations.
2. In case of a completely missing start date, the prior/concomitant therapy will be considered as having started before the trial.
3. In case of a completely missing end date, the prior/concomitant therapy will be considered as ongoing at the end of the trial.

4.8. Co-Infections

Data on viral (other than RSV) or bacterial pathogens determined in mid-turbinate nasal swabs collected at screening (both by multiplex PCR) will be listed.

Proportions of positive and negative results will be tabulated by treatment group.

5. EFFICACY

All efficacy will be analyzed on the ITT-i set. The primary endpoint will also be analyzed on mITT-i set and PP set.

The efficacy analyses include the following primary, secondary and exploratory endpoints.

Primary Endpoints

To explore the antiviral effect of JNJ-53718678 on RSV, as measured by qRT-PCR assay in mid-turbinate nasal swabs, the following virologic parameters will be assessed:

- AUC from immediately prior to first dose of study drug (baseline) through Day 3, Day 5, Day 8, and Day 14
- RSV viral load and change from baseline over time

- Time to undetectable RSV viral load
- Proportion of subjects with undetectable RSV viral load at each time point throughout the study.

Secondary Endpoints

- Clinical endpoints:
  - Duration and severity of signs and symptoms of RSV infection assessed through an instrument for patient-reported symptoms (either the Respiratory Infection-Patient Reported Outcomes [RI-PRO] questionnaire or the Respiratory Infection Intensity and Impact Questionnaire [RiiQ] questionnaire) and additional questions about health and functioning
  - Time to resolution of selected RSV symptoms as reported by the subject (through either the RI-PRO or RiiQ)
  - Respiratory rate, heart rate, body temperature, and SpO_2 as measured by the investigator.

Exploratory Endpoints

Exploratory endpoints include:

- Antiviral activity and clinical course by
  - time of symptom onset [≤3 days vs >3 days before randomization]
  - presence of comorbidities
  - baseline RSV viral subtype
  - severity of key RSV symptoms at screening, and
  - baseline RSV genotype
- The occurrence of complications associated with onset after treatment initiation that are associated with RSV per the investigator assessment:
  - Bacterial superinfections (eg, pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment)
  - Exacerbations of underlying pulmonary disease (eg, asthma, chronic obstructive pulmonary disease [COPD])
  - Exacerbations of underlying cardiovascular conditions
- The need for antibiotics related to complications associated with RSV per investigator assessment
- Sequence changes (post baseline) in the RSV F-gene, and other regions of the RSV genome (if applicable), as compared to baseline
- Medical resource utilization collected as medical encounters
- Association between clinical course of RSV and self-rated HRQOL (ie EQ-5D-5L).

5.1. Analysis Specifications

All efficacy summaries will be presented with descriptive statistics by treatment group and scheduled visit unless specified otherwise. In addition, descriptive summaries will be presented by the randomization stratification factor, time of symptom onset (≤3 days vs >3 days before randomization). If the endpoint is continuous, the descriptive statistics will include the number of subjects, mean standard deviation, standard error, median, range and interquartile range. If the endpoint is binary or categorical, the frequency distribution with the number and percentage of subjects in each category will be calculated.

For time to event variables, a summary table including number of subjects included in the analysis, number of subjects censored, 25th and 75th percentiles and median time-to event will be shown by treatment group.

For all the stratified statistical analyses, the derived randomization stratification factor will be used instead of the randomization stratification factor as collected in the IWRS.

5.1.1. Level of Significance

Since this is an exploratory, hypothesis-generating study, no hypothesis testing will be performed. However, two-sided 90% confidence intervals may be calculated without adjustments for multiplicity for comparing active dose groups versus placebo.

5.1.2. Data Handling Rules

Viral Load

Rule of maximum: Before any imputation is applied, the value for each Day is defined as the maximum value of all RSV assessments performed on that day. Please notice that this rule doesn't apply for baseline. For baseline details please see Section 2.1.2.

For analysis purposes, the $\log_{10}$ qRT-PCR viral load will be imputed with the midpoint on the log scale between the limit of detection and lower limit of quantification (LLOQ) when the result is 'target detected' (TD) but non-quantifiable.

- For the RSV-A qRT-PCR assay, the LOD is 620 copies/mL and the LLOQ is 1000 copies/mL, a result that is TD will be imputed with 2.90 $\log_{10}$ copies/mL.
- For the RSV-B qRT-PCR assay, the LOD is 80 copies/mL and the LLOQ is 250 copies/mL, a result that is TD will be imputed with 2.15 $\log_{10}$ copies/mL.

When the result is 'target not detected' (TND) (i.e., below the LOD), for both RSV A and RSV B the value of TND will be imputed with 0 $\log_{10}$ copies/mL.

For the overall analysis of viral load, all the viral load results of the RSV type with which the subject has been infected will be used.

In case of co-infection with both subtypes RSV A and B, the rules below will be applied for the overall analyses of viral load from the time the co-infection is detected (i.e. result of TD or >LLOQ):

- In case of two quantifiable results: the $\log_{10}$ of the sum of the RSV A and RSV B results in copies/mL will be used.
- In case of a quantifiable result and a TD/TND result: use the imputed TD/TND on the original scale and then use the $\log_{10}$ of the sum of the quantifiable result and the imputed value. copies/mL scale value and then use the $\log_{10}$ of the sum of the imputed value and quantifiable result.
- In case of two TD results, or one TD and one TND result: use the imputed TD/TND on the copies/mL scale values and then use the $\log_{10}$ of the sum of the imputed values.
- In case of two TND results: impute the TND as 0 $\log_{10}$.

5.2. Primary Efficacy Endpoints – Viral Load

5.2.1. Definition

To explore the antiviral effect of JNJ-53718678 on RSV, as measured by qRT-PCR assay in mid-turbinate nasal swabs, the following virologic parameters will be assessed:

- AUC from immediately prior to first dose of study drug (baseline) through Day 3 (48h), Day 5 (96h), Day 8 (168h), and Day 14 (312h);
- RSV viral load and change from baseline over time;
- Time to undetectable RSV viral load;
- Proportion of subjects with undetectable RSV viral load at each time point throughout the study.

The AUC viral load will be analyzed by two different methods:

- using a restricted maximum likelihood based repeated measures approach (mixed model)
- by trapezoidal method

Terminology is clarified in Table 11.

Table 11: AUC viral load

Method	
Mixed model	Trapezoidal
AUC Day 3	$AUC_{0\text{-}48h}$
AUC Day 5	$AUC_{0\text{-}96h}$
AUC Day 8	$AUC_{0\text{-}168h}$
	$AUC_{0\text{-}312h}$

Formulae to be used for derived variables, including data conversions, are provided in the table below. Note that for time-to-event variables the actual dates will be used.

Measurement	**Formula**
Log_{10} viral load actual values	Log_{10} of the actual values as measured with qRT-PCR, including both swabs collected at the clinic visits and at home.
Log_{10} viral load change from baseline	Change = Log_{10} viral load actual value – log_{10} baseline value
RSV viral load $AUC_{0\text{-}48h}$ [trapezoidal method]	RSV viral load $AUC_{0\text{-}48h}$ from 0 hours until 48 hours (Day 3) using the trapezoidal method (see below).
RSV viral load $AUC_{0\text{-}96h}$ [trapezoidal method]	RSV viral load $AUC_{0\text{-}96h}$ from 0 hours until 96 hours (Day 5) using the trapezoidal method (see below).
RSV viral load $AUC_{0\text{-}168h}$ [trapezoidal method]	RSV viral load $AUC_{0\text{-}168h}$ from 0 hours until 168h (Day 8) hours using the trapezoidal method (see below).
RSV viral load $AUC_{0\text{-}312h}$ [trapezoidal method]	RSV viral load $AUC_{0\text{-}312h}$ from 0 hours until 312h (Day 14) hours using the trapezoidal method (see below).

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td>Time to virus undetectable (hours)

[Time-to event]</td><td>Time to virus undetectable will be evaluated using two approaches:

1) The time in hours from initiation of study treatment until the first post-baseline time point at which the virus is undetectable and after which time, no more detectable virus assessment (= event).

<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last recording baseline assessment</td><td>time 0h</td></tr>
<tr><td>Last available assessment is detectable</td><td>(right-censored) at last available assessment</td></tr>
</table>
2) The time in hours from initiation of study treatment until the first post-baseline time point at which the virus is confirmed undetectable (=event).

A confirmed undetectable sample is defined as the first of at least, two consecutive undetectable virus assessments.

Last obtained sample is always considered confirmed**.**

<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last record is baseline assessment</td><td>time 0h</td></tr>
<tr><td>Last available assessment is detectable</td><td>(right-censored) at last available assessment</td></tr>
</table>

(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal.</td></tr>
<tr><td>Viral load status at each time point (categorical)</td><td>Each RSV viral load measurement will be assigned to one of the 3 categories below:
Undetectable (TND)
Detectable (TD)
Quantifiable</td></tr>
<tr><td>Viral load status at each time point (binary)</td><td>Each RSV viral load measurement will be assigned to one of the 2 categories to identify if it is detectable.
• Detectable or quantifiable = Yes (1)
• Undetectable = No (0)</td></tr>
</table>

The trapezoidal method will be used to calculate viral load AUC between 0 and xx hours, based on date times of sampling, including the timepoints with (imputed) values available:

$$AUC_{0-\text{xx } hours} = \frac{1}{2}\sum_{i=1}^{n}(y_i + y_{i-1}) \times (t_i - t_{i-1})$$

where i=1,2,3,… are the time points when post baseline samples are collected, y_i is the $\log_{10}$ viral load at the time t_i and t_i is the time in hours post baseline. y_o is the (imputed) $\log_{10}$ viral load at baseline, t_0 is time 0 hours, t_n is time xx.

The following rules will be applied to deal with missing values before calculating the viral load AUC:

1. The value at time point 0h, if not exactly at 0h, will be calculated based on linear interpolation between the last observed pre-dose value and the first observed post-dose value.
2. In case the first available observation is after 0 hours, the value at 0h will be imputed by carrying backward the first available observation.
3. The value at xx hours, if not exactly at xxh, will be calculated based on interpolation between the last observed value before xxh and the first observed value after xxh.
4. In case the last available observation is before xxh, the value at xxh will be imputed by carrying forward the last available observation. Carrying forward should only be performed if the time between the available observation and the value at xxh is at most 24 hours.
5. Missing values between 0h and xxh will be imputed by interpolation (automatically by trapezoidal rule).
6. In case the last observation is before xxh, and the value at xxh cannot be determined, the AUCs through xxh and through any later timepoint will not be derived.

Note that additionally the AUC will be derived using a mixed model approach.

5.2.2. Analysis Methods

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach. Analysis will include fixed categorical effects of treatment, strata (symptoms onset [≤3 days vs >3 days before randomization), visit, treatment-by-visit interaction, and the continuous covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load-by-visit interaction as well as a random effect to model the within-subject error covariance. An unstructured covariance structure will be selected. In case this model will not converge, the Toeplitz covariance structure will be applied. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

No imputations of missing data from nasal swabs post-baseline will be done in this model, as this mixed model would allow to make inferences under the *missing at random* assumption. Note that for this analysis only values as provided by the central lab will be used.

To evaluate the difference in the AUC between active and placebo, 3 contrasts will be explored: a contrast with no difference between the 2 active doses tested against placebo; a contrast with no difference between low dose and placebo tested against high dose; and a contrast with a linear

dose-response relationship with respect to the active doses. These contrasts will be used to derive the least square mean differences in the AUCs for active versus placebo, and their 90%CIs, with no multiplicity correction.

RSV RNA Viral Load

Descriptive statistics, mean (SE) graphs and median (IQR) graphs will be shown for the log_{10} viral load actual values and changes from baseline by visit and by treatment group.

Differences on RSV RNA log_{10} viral load by qRT PCR between treatment groups and by analysis visit will be determined by using appropriate contrasts in a similar repeated measure mixed effects model, including 90% 2-sided confidence intervals.

The potential associations with RSV RNA log_{10} viral load and the following covariates and/or baseline indicators will be explored graphically:

- baseline log_{10} viral load
- smoking history (never/current/former)
- history of wheezing (yes/no)
- presence/absence of comorbid diseases associated with risk for severe RSV disease
- presence/absence of other conditions/therapy of potential interest
- days since symptom initiation (0,1,2,3,4,5)
- RSV subtype
- use of corticosteroids
- supplemental oxygen at baseline
- age as continuous variable.
- severity of key RSV symptoms at screening
- baseline RSV genotype;

The homogeneity of treatment effect on the occurrence of AUC viral load from baseline to Days 3, 5, and 8 across subgroups will be examined using the same MMRM model approach for the primary analysis, but also includes the subgroup-by-treatment and subgroup-by-visit interaction terms in the model. A forest plot will present the Least Square means and 90% CI for all subgroups of interest.

RSV Viral Load AUC

The individual AUC as calculated using the trapezoidal rule will be considered as a supportive analysis and will be analyzed using a linear model with AUC as a dependent variable and treatment group and stratum as fixed factor and baseline log_{10} viral load as covariate. The differences versus placebo will be estimated using appropriate contrasts with 90% 2-sided confidence intervals.

Time to virus undetectable [time-to event]

Time-to event variable will be analyzed and plotted using Kaplan-Meier estimates analysis. The estimate of the hazard ratio (HR) and the 90% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (derived randomization stratification factor: ≤3 days, >3 days) and including treatment group as a covariate.

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 90% confidence intervals based on the Kaplan-Meier method, will be presented by treatment group.

First approach to evaluate virus undetectable, as described in Section 5.2.1 will considered for this analysis.

The potential impact of selected variables that identify the subgroups of interest on the time to virus undetectable will be assessed by the stratified Cox proportional hazard model. The model will be stratified by the randomization stratification factors and include treatment group and subgroup variable as covariates, and the subgroup by treatment interaction term. A forest plot will present the HRs and 90% CI for all subgroups of interest.

Proportion of subjects with undetectable RSV viral load

The proportion of subjects within the RSV RNA viral load categories (undetectable, detectable and quantifiable) will be shown in a frequency tabulation, by treatment group and visit. Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion. The difference in proportions for undetectable versus detectable/quantifiable between each active group and placebo, will be tabulated descriptively (n and % per treatment group), for each post baseline timepoint. Summaries of the difference between groups will include 2-sided 90% confidence intervals based on the Wilson score test.

In case of co-infection with both RSV A and B, the worst category will be used for the analysis. As higher viral loads so denote worse degree of infection, the ordering will be from worst to better namely quantifiable – detectable – undetectable.

Information will also be presented graphically.

5.3. Secondary Endpoints - Clinical Course

Clinical course related endpoints are as follows:

- Duration and severity of signs and symptoms of RSV infection assessed through either the Respiratory Infection Patient Reported Outcome (RI-PRO) or the Respiratory Infection Intensity and Impact Questionnaire [RiiQ] questionnaire, and Additional Questions about Health and Functioning.
- Time to resolution of selected RSV symptoms as reported by the subject through either the RI-PRO or RiiQ.
- Respiratory rate, heart rate, body temperature, peripheral capillary oxygen saturation (SpO_2) as measured by the investigator.

5.3.1. Definition

5.3.1.1. ePROs

RI-PRO, RiiQ, and Additional Questions about Health and Functioning and EQ-5D-5L will be collected from Screening to Day 21. RI-PRO, RiiQ, and Additional Questions about Health and Functioning are completed twice daily (morning and evening) from Day 1 to Day 13.

Note: RiiQ will be completed only by subjects enrolled after the approval of Protocol-Amendment 1. These subjects will complete RI-PRO only at Screening/Baseline and Day 8.

Considering the two scales (RI-PRO and RiiQ) used in the study, the below table reflects the one to one mapping of the key RSV symptom items in RI-PRO to those of the RiiQ that will be used in the analyses.

The RI-PRO key RSV symptoms are as follows: congested or stuffy nose, sore or painful throat, trouble breathing, chest tightness, coughing, coughed up mucus or phlegm, weak or tired.

The RiiQ key RSV symptoms are as follows: nasal congestion, sore throat, short of breath, wheezing, cough, coughing up phlegm (sputum), fatigue (tiredness).

RI-PRO domain	RI-PRO items **(key items)**	RiiQ symptom domain items **(key items)**
Nose	Runny or dripping nose **Congested or stuffy nose** Sneezing Sinus pressure	**Nasal congestion**
Throat	Scratchy or itchy throat **Sore or painful throat** Difficulty swallowing	**Sore throat**
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	
Chest/Respiratory	**Trouble breathing** Chest congestion **Chest tightness** Dry or hacking cough Wet or loose cough **Coughing** **Coughed up mucus or phlegm**	**Wheezing** **Short of breath** **Cough** **Coughing up phlegm (sputum)**
Gastrointestinal	Felt nauseous Stomach ache Vomit (frequency) Diarrhea (frequency)	

Body/Systemic	Felt dizzy	
	Head congestion	
	Headache	Headache
	Lack of appetite	Loss of appetite
	Sleeping more than usual	Interrupted sleep
	Body aches or pains	Body aches and pains
	Weak or tired	**Fatigue (tiredness)**
	Chills or shivering	Feeling feverish
	Felt cold	
	Felt hot	
	Sweating	
		Neck pain

Formulae to be used for derived variables, including data conversions, are provided in the table below. Note that for time-to-event variables the actual date times will be used.

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td colspan="2">PATIENT REPORTED OUTCOMES</td></tr>
<tr><td colspan="2">RI-PRO</td></tr>
<tr><td>RI-PRO domain scores + change from baseline</td><td>RI-PRO is a 32 items questionnaire computed in six domain scores, representing symptom severity in each of the following body areas as follows:
<table>
<tr><th>Domain</th><th>Score calculation</th></tr>
<tr><td>Nose</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 3 out of 4 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Throat</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 2 out of 3 items are available</td></tr>
<tr><td>Eyes</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 2 out of 3 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Chest/ Respiratory</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 5 out of 7 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Gastrointestinal</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 3 out of 4 items are available, otherwise it will be set to</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>missing.</td></tr>
<tr><td>Body/Systemic</td><td>Arithmetic mean of the available items.
Score will be calculated if at least 8 out of 11 items are available, otherwise it will be set to missing.</td></tr>
</table>
Each RI-PRO domain score ranges from 0 (symptom free) to 4 (very severe symptoms)

Please see Attachment [3].</td></tr>
<tr><td>RI-PRO key symptom score + change from baseline</td><td>Arithmetic mean of the following 7 key items (congested or stuffy nose, sore or painful throat, trouble breathing, chest tightness, coughing, coughed up mucus or phlegm, weak or tired) will be calculated if at least 5 out of 7 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Daily average RI-PRO domain scores + change from baseline</td><td>The worst result observed for each of the items within a domain, will be used to calculate the average of the RI-PRO domain scores per day (in case of BID)</td></tr>
<tr><td>Time to resolution of selected RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until the first time of resolution of RSV symptoms.

Resolution of RSV symptoms occurs when items within a selected domain in the RI-PRO are scored as ‘Not at all’ (score = 0) or ‘A little bit’ (score =1) (ie alleviated) for at least 24 hours.

Selected domains to consider are nose, throat, chest/respiratory and body/systemic symptoms.

• Three consecutive recordings indicating resolution are required, if the first (of these 3 consecutive) recording is <u>before</u> the second analysis timepoint of the BID schedule at Day 13. These 3 consecutive recordings should have been done over 4 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed.
• Two consecutive recordings indicating resolution are required, if the first (of these 2 consecutive) recording is <u>at or after</u> the second analysis timepoint of the BID schedule at Day 13. These 2 consecutive recordings should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed

In case RSV symptoms are not resolved, data will be censored.

<u>Censoring will be done as follows</u>:
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last record(s) indicate</td><td>first record of resolution from</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
<table>
<tr><td>resolution of RSV symptoms but insufficient recordings to meet the time to resolution</td><td>the last series of recordings of resolution of RSV symptoms</td></tr>
<tr><td rowspan="2">Last record does not indicate resolution of RSV symptoms</td><td>after the last observation, at 20:00 on the same day if the last observation was a morning diary entry (from 02:00 until 13:59)</td></tr>
<tr><td>at 8:00 the next day if the last entry was an evening diary (from 14:00 until 01:59)</td></tr>
<tr><td>Death (without previous resolution)</td><td>date of death.
If time is not available, it will be imputed as per 00:01 of the date of death</td></tr>
<tr><td>missing information to determine resolution or resolution of symptoms because of hospitalization</td><td>date of hospitalization
If time is not available, it will be imputed as per 00:01 of the date of hospitalization</td></tr>
</table>
(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
</td></tr>
<tr><td>Time to complete resolution of selected RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until first complete resolution of RSV symptoms.
Complete resolution of RSV symptoms occurs when items within a selected domain in the RI-PRO are scored as ‘Not at all’ (score = 0) for at least 24 hours.
Censoring will be applied as defined above.</td></tr>
<tr><td>Time to resolution of all RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until the first time of resolution of RSV symptoms.
Resolution of RSV symptoms occurs when all items within a domain in the RI-PRO are scored as ‘Not at all’ (score=0) or ‘A little bit’ (score =1) (ie alleviated) for at least 24 hours.
Censoring will be applied as defined above.</td></tr>
<tr><td>Time to complete resolution of all RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until first complete resolution of all RSV symptoms.
Complete resolution of RSV symptoms occurs when all items within a domain in the RI-PRO are scored as ‘Not at all’ (score = 0) for at least 24 hours.</td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>Censoring will be applied as defined above.</td></tr>
<tr><td>Time to resolution of key RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until the first time of resolution of key RSV symptoms.

Resolution of key RSV symptoms occurs when all 7 key items are scored as ‘Not at all’ (score = 0) or ‘A little bit’ (score =1) (ie alleviated) for at least 24 hours.

Censoring will be applied as defined above.</td></tr>
<tr><td>Time to complete resolution of key RSV symptoms from RI-PRO (hours) [Time-to event]</td><td>Time (in hours) from first dose of study drug until complete resolution of all 7 key RSV symptoms.

Complete resolution of key RSV symptoms occurs when all items within a domain in the RI-PRO are scored as ‘Not at all’ (score = 0) for at least 24 hours.

Censoring will be applied as defined above.</td></tr>
<tr><td colspan="2">RiiQ</td></tr>
<tr><td>RiiQ symptom score + change from baseline</td><td>RiiQ symptom domain is a 13 items questionnaire which ranges from 0 (symptom free) to 3 (severe symptoms). Arithmetic mean will be calculated if at least 9 out of 13 items are available, otherwise it will be set to missing.
Please see Attachment [3].</td></tr>
<tr><td>RiiQ key symptom score + change from baseline</td><td>Arithmetic mean of the following 7 key items (nasal congestion, sore throat, short of breath, wheezing, cough, coughing up phlegm [sputum], fatigue [tiredness]) will be calculated if at least 5 out of 7 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Daily average RiiQ symptom score + RiiQ key symptom score + change from baseline</td><td>The worst result observed for each of the items will be used to calculate the average of the RiiQ symptom score per day (in case of BID).</td></tr>
<tr><td>RiiQ impact scores + change from baseline</td><td>There are 3 RiiQ impact domains: Daily activity (7 items), Emotions (4 items), and Relationship (5 items). Each item ranges from 0 (no impact) to 3 (severe impact).
<table>
<tr><th>Domain</th><th>Score calculation</th></tr>
<tr><td>Daily activity</td><td>Arithmetic mean will be calculated if at least 5 out of 7 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Emotions</td><td>Arithmetic mean will be calculated if at least 3 out of 4 items are available, otherwise it will be set to missing.</td></tr>
<tr><td>Relationship</td><td>Arithmetic mean will be calculated if at</td></tr>
</table></td></tr>
</table>

Measurement	Formula
	least 3 out of 5 items are available, otherwise it will be set to missing.
Time to resolution of all RSV symptoms from RiiQ (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of all RSV symptoms. Resolution of RSV symptoms occurs when all items within the symptom domain of RiiQ are scored as 'None' (score = 0) or 'Mild' (score =1) for at least 24 hours. Censoring will be applied as defined above.
Time to complete resolution of all RSV symptoms from RiiQ (hours) [Time-to event]	Time (in hours) from first dose of study drug until first complete resolution of all RSV symptoms. Complete resolution of RSV symptoms occurs when all items within the symptom domain of the RiiQ are scored as 'None' (score = 0) for at least 24 hours. Censoring will be applied as defined above.
Time to resolution of key RSV symptoms from RiiQ (hours) [Time-to event]	Time (in hours) from first dose of study drug until the first time of resolution of all 7 key RSV symptoms. Resolution of key RSV symptoms occurs when all 7 key items within the symptom domain of the RiiQ are scored as 'None' (score = 0) or 'Mild' (score =1) for at least 24 hours. Censoring will be applied as defined above.
Time to complete resolution of key RSV symptoms from RiiQ (hours) [Time-to event]	Time (in hours) from first dose of study drug until first complete resolution of all 7 key RSV symptoms. Complete resolution of RSV symptoms occurs when all 7 key items within the symptom domain in the RiiQ are scored as 'None' (score = 0) for at least 24 hours. Censoring will be applied as defined above.
Common endpoints for RI-PRO and RiiQ	
Key RSV symptom score from either RI-PRO or RiiQ + daily average + change from baseline	Arithmetic mean of the key items from either RI-PRO or RiiQ will be calculated if at least 10 out of 14 items are available, otherwise it will be set to missing. When a key item is available in both RI-PRO and RiiQ, only the key item from RiiQ will be considered. The worst result observed for each of the items will be used to calculate the average of the RI-PRO or RiiQ symptom score per day (in case of BID).
Time to resolution of key RSV symptoms (hours) from either RI-PRO or	Time (in hours) from first dose of study drug until the first time of resolution of all 7 key RSV symptoms from either RI-PRO or

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td>RiiQ [Time-to event]</td><td>RiiQ.

Resolution of key RSV symptoms occurs when all 7 key items from either RI-PRO or RiiQ are scored as 0 or 1 (ie alleviated) for at least 24 hours.

Censoring will be applied as defined above.</td></tr>
<tr><td>Time to complete resolution of key RSV symptoms (hours) from either RI-PRO or RiiQ [Time-to event]</td><td>Time (in hours) from first dose of study drug until complete resolution of all 7 key RSV symptoms from either RI-PRO or RiiQ.

Complete resolution of all 7 key RSV symptoms occurs when all 7 key items from either RI-PRO or RiiQ are scored as 0 for at least 24 hours.

Censoring will be applied as defined above.</td></tr>
<tr><td colspan="2">Additional Questions About Health and Functioning</td></tr>
<tr><td>Additional questions about health and functioning</td><td>Nine items (please see Attachment [3]) about health and functioning.</td></tr>
<tr><td>Time to return to usual activity (hours) [Time-to-event]</td><td>Time (in hours) from the first dose of study drug until the time of return to usual activity.

Return to usual activity occurs when the response is ‘Yes’ on RI-PRO additional question 7 (“Have you returned to your usual activities today?”) for at least 24 hours.

• Three consecutive recordings are required, if the first (of these 3 consecutive) recording is <u>before</u> the second analysis timepoint of the BID schedule at Day 13. These 3 consecutive recordings should have been done over 4 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed.
• Two consecutive recordings are required, if the first (of these 2 consecutive) recording is <u>at or after</u> the second analysis timepoint of the BID schedule at Day 13. These 2 consecutive recordings should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed

In case return to usual activity is not reached, data will be censored.

<u>Censoring will be done as follows</u>:
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last record(s) indicate return to usual activity but insufficient recordings to meet</td><td>first record of return from the last series of recordings of return to usual activity.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
<table>
<tr><td>the time to return to usual activity</td><td></td></tr>
<tr><td>Last record does not indicate return to usual activity</td><td>after the last observation, at 20:00 on the same day if the last observation was a morning diary entry (from 02:00 until 13:59)</td></tr>
<tr><td></td><td>at 8:00 the next day if the last entry was an evening diary (from 14:00 until 01:59)</td></tr>
<tr><td>Death (without previous return to usual activity)</td><td>date of death.
If time is not available, it will be imputed as per 00:01 of the date of death</td></tr>
<tr><td>missing information to determine return to usual activity because of hospitalization</td><td>date of hospitalization
If time is not available, it will be imputed as per 00:01 of the date of hospitalization</td></tr>
</table>
(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
</td></tr>
<tr><td>Time to return to usual health (hours) [Time-to-event]</td><td>Time (in hours) from the first dose of study drug until the time of return to usual health.

Return to usual health occurs when the response is ‘Yes’ on RI-PRO additional question 9 (“Have you returned to your usual health today?”) for at least 24 hours.

• Three consecutive recordings are required, if the first (of these 3 consecutive) recording is <u>before</u> the second analysis timepoint of the BID schedule at Day 13. These 3 consecutive recordings should have been done over 4 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed.
• Two consecutive recordings are required, if the first (of these 2 consecutive) recording is <u>at or after</u> the second analysis timepoint of the BID schedule at Day 13. These 2 consecutive recordings should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed

In case return to usual health is not reached, data will be censored.

<u>Censoring will be done as follows</u>:</td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last record(s) indicate return to usual health but insufficient recordings to meet the time to return to usual health</td><td>first record of return from the last series of recordings of return to usual health.</td></tr>
<tr><td rowspan="2">Last record does not indicate return to usual health</td><td>after the last observation, at 20:00 on the same day if the last observation was a morning diary entry (from 02:00 until 13:59)</td></tr>
<tr><td>at 8:00 the next day if the last entry was an evening diary (from 14:00 until 01:59)</td></tr>
<tr><td>Death (without previous return to usual health)</td><td>date of death.
If time is not available, it will be imputed as per 00:01 of the date of death</td></tr>
<tr><td>missing information to determine return of usual health because of hospitalization</td><td>date of hospitalization
If time is not available, it will be imputed as per 00:01 of the date of hospitalization</td></tr>
</table>
(Date and time of event or censoring - date and time of first dose of study drug)/3600, rounded to one decimal
</td></tr>
<tr><td colspan="2">5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)</td></tr>
<tr><td>EQ-5D dimension parameters:
Mobility,
Self-care,
Usual activities,
Pain/discomfort,
Anxiety/depression</td><td>EQ-5D is questionnaire composed by the following dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/ depression, each of them with a level score from 1 to 5.
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)).
Please see Attachment [4]: EQ-5D-5L for further details.</td></tr>
<tr><td>EQ-5D VAS</td><td>EQ-5D VAS is a continuous score ranging from 0 (worst health you can imagine) to 100 (best health you can imagine).</td></tr>
<tr><td>EQ-5D Valuation index</td><td>EQ-5D Valuation index summarizes the information of the</td></tr>
</table>

Measurement	Formula
	5 dimensions of the descriptive system. o Assign the level code 1, 2, 3, 4 and 5 to each level of the 5 dimensions (see Attachment [4]: EQ-5D-5L) o 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 walking, slight problems washing or dressing myself, unable to do my usual activities, severe pain or discomfort, moderately anxious or depressed'. Assign an index value to each health state as defined in Respiratory 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.

5.3.1.2. Clinical Course Endpoints related to Respiratory, Heart Rate and Body Temperature

5.3.1.2.1. Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature

Measurement	Formula
Clinical Course Endpoints related to Respiratory, Heart Rate and Body Temperature	
Respiratory Rate actual values + changes from baseline	Actual values of Respiratory Rate measured at baseline/Day 1, Day 3, Day 8, Day 14 and Day 21.
Respiratory Rate status at each visit (binary)	Each measurement will be assigned to one of the 2 categories to identify if the respiratory rate is normalized to the pre-RSV disease status, rated by the investigator at baseline/Day 1, Day 3, Day 8, Day 14 and Day 21. Normalization of respiratory rate (RR) will be derived from the answer to the corresponding question in the eCRF "Is this value similar to the pre-RSV infection value for this patient?" • Yes → Normalized (0)

Measurement	**Formula**
	• No → Abnormal (1)
Heart Rate actual values + changes from baseline	Heart Rate measured at baseline, Day 3, Day 8, Day 14 and Day 21.
Heart Rate status at each visit (binary)	Each measurement will be assigned to one of the 2 categories to identify if the heart rate is normalized to the pre-RSV disease status, rated by the investigator at baseline, Day 3, Day 8, Day 14 and Day 21. Normalization of heart rate (HR) will be derived from the answer to the corresponding question in the eCRF "Is this value similar to the pre-RSV infection value for this patient?" • Yes → Normalized (0) • No → Abnormal (1)
Oxygen Saturation actual values + changes from baseline	Oxygen Saturation measured at baseline, Day 3, Day 8, Day 14 and Day 21.
Oxygen Saturation status at each visit (binary)	Each measurement will be assigned to one of the 2 categories to identify if the oxygen saturation is normalized to the pre-RSV disease status, rated by the investigator at baseline/Day 1, Day 3, Day 8, Day 14 and Day 21. Normalization of oxygen saturation (SpO2) will be derived from the answer to the corresponding question in the eCRF "Is this value similar to the pre-RSV infection value for this patient?" • Yes → Normalized (0) • No → Abnormal (1)
Body Temperature actual values + changes from baseline	Body Temperature measured at on-site clinic visits (baseline, Day 3, Day 8, Day 14 and Day 21), as well as measured at home.

5.3.1.2.2. Other Clinical Course Parameters

Measurement	**Formula**
Other Clinical Course Parameters	
Need for Oxygen supplementation	Subjects who required supplemental oxygen after first dose of study drug and who's answer to the question "Has supplemental oxygen administration returned to that level provided prior to the current respiratory infection?" is 'No', will receive code 1. Subjects who did not require supplemental oxygen or for who the level returned to the level provided prior to the current respiratory infection, will receive code 0.
Respiratory infection complication	Subjects who experienced a respiratory infection complication after first dose of study drug will receive code 1, subjects who did not experience a complication will receive code 0. The overall category will consist of any complication (answer to the question: "Is this AE a complication related to the current respiratory infection?"). The following subcategories will also be analyzed: ▪ Respiratory complications, including o Bacterial complications o Viral complications ▪ Non-respiratory infectious complications, including o Bacterial complications o Viral complications ▪ Metabolic complications ▪ Other
Wheezing status	Investigator will evaluate the subject's wheezing at on-site visits Screening/baseline, Day 3, Day 8, Day 14 and Day 21 as per information collected in the eCRF under: "Describe the subject's wheezing now" • No wheezing • Terminal expiratory wheezing or only with stethoscope • Entire expiration or audible during expiration without stethoscope • Inspiration and expiration without stethoscope

Measurement	Formula
	"On auscultation are the following present" • Rales (crackles) → Yes/No • Ronchi → Yes/No

5.3.2. Analysis Methods

5.3.2.1. Endpoint-specific analysis methods

RI-PRO and RiiQ domain scores and daily average domain scores

Descriptive statistics, mean (SE) graphs and median (IQR) graphs will be shown for the actual values and changes from baseline for both Ri-PRO and RiiQ scores.

Changes from baseline on each of the RI-PRO and RiiQ domain scores will be analyzed using a restricted maximum likelihood based repeated measures approach as per Section 5.2.2. An unstructured covariance structure will be selected.

Additional Questions about Health and Functioning

Frequency tabulations for the 9 additional questions about health and functioning will provided.

EQ-5D-5L VAS

Frequency tabulations of the EQ-5D-5 L dimensions will be provided.

EQ-5D VAS descriptive statistics for the actual values and changes from baseline will be summarized.

Changes from baseline at each day of assessment will be analyzed using a restricted maximum likelihood based repeated measures approach as per Section 5.2.2. An unstructured covariance structure will be selected.

Respiration Rate, Heart Rate, Oxygen Saturation and Body Temperature

Descriptive statistics, mean (SE) graphs and median (IQR) graphs will be shown for the actual values and changes from baseline by visit and by treatment group.

Respiration Rate Status, Heart Rate Status and Oxygen Saturation Status

The proportion of subjects within the two categories (abnormal, normalized) for each status (respiration rate, heart rate, and oxygen saturation) will be shown in a frequency tabulation by treatment group and analysis time point. The difference in proportions for abnormal status between each active group and placebo will be tabulated, and summaries will include 2-sided 90% confidence intervals based on the Wilson score test.

Subjects with missing data on that analysis visit will not be counted in the denominator for the proportion.

Need of Oxygen supplementation

The requirement for oxygen supplementation will only be calculated for those subjects that don't require oxygen supplementation before first dose of study drug.

The proportion of subjects with oxygen supplementation (yes and no) will be shown in a frequency tabulation by treatment group. The difference in proportions between each active group and placebo will be tabulated, summaries will include 2-sided 90% confidence intervals based on the Wilson score test.

Note that these incidences are only analyzed if any subjects require oxygen supplementation.

Respiratory infection complication

The proportion of subjects with presence/absence of complications (overall category and subcategories) will be shown in a frequency tabulation by treatment group including a column for the total JNJ-8678 irrespective of the doses.

Note that these incidences are only analyzed if any subjects have complications occur.

Time to resolution of symptoms, Time to return to usual health and Time to return to usual activity

Time-to event variable will be analyzed and plotted using Kaplan-Meier estimates analysis. The estimate of the hazard ratio (HR) and the 90% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (derived randomization stratification factor: ≤3 days, >3 days) and including treatment group as a covariate. Due to limited available RiiQ data, these analyses will not be applied to the RiiQ time to event variables.

A summary table including number of subjects included in the analysis, number of subjects censored, 25^{th} and 75^{th} percentiles and median time-to event, with 90% confidence intervals based on the Kaplan-Meier method, will be presented by treatment group.

The potential impact of selected variables that identify the subgroups of interest on the time to resolution of symptoms will be assessed by the stratified Cox proportional hazard model. The model will be stratified by the randomization stratification factors and include treatment group and subgroup variable as covariates, and the subgroup by treatment interaction term. A forest plot will present the HRs and 90% CI for all subgroups of interest.

Breathing Sounds

Frequency tabulations of each wheezing status will be provided by treatment group and visit.

The proportion of subjects with Rales and Ronchi (yes and no) will be shown in a frequency tabulation by treatment group. The difference in proportions between each active group and

placebo will be tabulated, summaries will include 2-sided 90% confidence intervals based on the Wilson score test.

5.4. Sensitivity Analyses

As a sensitivity analysis, the analysis on change from baseline on Day 3 and Day 8 will be repeated but excluding viral load data not collected by a Health Care Professional (HCP). If different results will be observed from this sensitivity and the primary analysis, then additional analyses may be performed to investigate further.

Time to virus undetectable will be also repeated but considering the second approach (please see Section 5.2.1) to evaluate virus undetectable.

Sensitivity analyses to assess the robustness of the primary efficacy analysis of viral load AUC will be performed by including the stratification factor, RSV symptom onset (≤3 days or > 3 days), as collected by the IWRS in the mixed-effects model. Additionally, the primary efficacy analysis will be repeated on the mITT-I set.

For the time to resolution of selected RSV symptoms of RI-PRO, sensitivity analyses will be performed considering 4 different imputation methods:

- Method 1: from first resolution (score 0 or 1) after last unresolved value onwards, impute missing data as resolution.
- Method 2: impute all missing values as unresolved (score >1).
- Method 3: impute all missing values in-between resolved observations (score 0 or 1) as resolved.
- Method 4: impute all missing values as unresolved (score >1), except when in-between resolved values where resolved is imputed.

5.5. Other Efficacy Variable(s)

5.5.1. Definition

Measurement	**Formula**
Need for antibiotics related to complications associated with RSV	Need for antibiotics is defined as 'Yes' if the answers to the following 4 questions on the AE page in the eCRF are answered with 'Yes' to all of them. • Is this AE a complication related to the current respiratory infection? • Is this an infection? • If yes, was infection treated with oral or parenteral antibiotics? If yes, specify the type of complication "Respiratory Complications"

5.5.2. Analysis Methods

Summary tables will be presented by treatment group, stratification factor and visits.

Need for antibiotics related to complications associated with RSV

The proportion of subjects with a need for antibiotics (yes and no) will be shown in a frequency tabulation. The difference in proportions between each active group and placebo will be tabulated, summaries will include 2-sided 90% confidence intervals based on the Wilson score test

5.6. Exploratory Analyses

Relationships between primary antiviral effect endpoints and clinical course endpoints will be investigated as follows

Antiviral activity endpoints:

- RSV RNA $\log_{10}$ viral load AUCs.
- Time to virus undetectable.
- Time to virus confirmed undetectable

Clinical course endpoints:

- RI-PRO score per domain
- Key RSV symptom score from RI-PRO
- Key RSV symptom score from either RI-PRO or RiiQ (if available RiiQ data)
- Time to resolution of selected RSV symptoms from RI-PRO
- Time to resolution of key RSV symptoms from RI-PRO
- Time to resolution of key RSV symptoms from either RI-PRO or RiiQ (if available RiiQ data)
- Time to resolution of all RSV symptoms from RI-PRO
- EQ-5D-5L each dimension and Visual Analog Scale

The relationships for each pair of variables described above will be explored using the Spearman's rank correlation coefficients. Scatterplots with smoother curve per treatment group will be used for continuous and time-to-event variables (ignoring censoring). Boxplots will be created to graphically present the association between continuous and binary variables. For association between time-to-event clinical course parameters and continuous or binary variables, Kaplan-Meier plots will be generated by quartiles of the continuous variable, or by yes/no status of the binary variable, respectively.

The association between each EQ-5D-5L dimension and time to alleviation will also be explore using the spearman's rank correlation coefficient and graphically.

6. SAFETY

All safety analyses will be done on the Safety Set.

6.1. Adverse Events

All safety analyses will be done on the Safety Set.

6.1.1. 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.

Emergent Adverse Event

Emergent AEs are AEs with onset after first study medication intake or that are a consequence of a pre-existing condition that has worsened since baseline. All reported emergent AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Phase allocation of AE

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

Incomplete dates (i.e. time and/or day and/or month and/or year missing) are imputed according to the rules in Section 2.5.

6.1.2. Analysis Methods

Treatment-emergent adverse events will be summarized by body system, preferred term and treatment group (including a column for total JNJ-8678).

A summary will be provided for the following emergent adverse events by phase (treatment phase, follow-up phase) and by treatment:

- any adverse events,
- serious adverse events,
- deaths due to AE,
- adverse events by toxicity grade,
- AEs at least possibly related to study medication,
- AEs for which study medication was permanently stopped,
- AEs for which study was discontinues prematurely.
- serious adverse events that were at least possibly related to study medication.

There will be no formal statistical testing.

Incidence tabulations will be provided for individual adverse events in the above categories (in case there are at least 5 events). Additionally, tabulation of AEs of at least grade 2 and considered related to study drug will be provided.

Listings will be provided for at least the following categories: all AEs, serious AEs, AEs leading to death, AEs leading to permanent stop, grade 3-4 AEs.

The summary, incidence tabulation for the individual preferred terms and subject listing will be provided for the RSV-related complications.

The following adverse events will be tabulated; or listed (in case there are less than 5 events) by subgroups (see Section 2.4): any AE, any RSV-related complications, any grade 3-4 AE, AEs that are at least possibly related to study medication, AEs leading to death, serious AEs, AEs leading to permanent stop of study medication.

6.2. Clinical Laboratory Tests

6.2.1. 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.

Coagulation function will be monitored during this study through evaluation of partial thromboplastin time (PTT) activated partial thromboplastin time (aPTT) in seconds and of the International normalized ratio.

Renal Function will be monitored during the study through evaluation of the estimated Glomerular Filtration (eGFR) based on:

- Serum creatinine by Cockcroft-Gault formula
  C_{Cr} (mL/min) = sex * [(140 - age) * weight(kg) / 72 * S_{Cr}(mg/dL)]; if female, correction factor is 0.85
- Serum cystatin C
  GFR (mL/min/1.73m^2) = 84.69 * cystatin C (mg/L)$^{-1.680}$

Toxicity grades and abnormalities for laboratory parameters:

The laboratory abnormalities will be determined according to the DMID adult toxicity grading scale (see Attachment [3]), available toxicity grades provided by the central lab (Covance) will 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), including unscheduled measurements.
- 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 means that the sum of the percentages can be more than 100%).
- If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations.

Emergent definition for toxicity grades and abnormalities

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

In case of missing date or partial dates

Laboratory records with missing assessment date- or partially missing (any: day, month or year) will not be used in descriptive statistics, unless the scheduled target day or time is known, and a unique phase allocation is possible taking this additional information into account. These assessments will be allocated to the correct phase using the available date information, and the information on their assessment schedule. In case it is not possible to assign a unique phase (e.g. unscheduled time points), the assessment will be assigned to all possible active phases based on the available date and time information. These cases will be flagged in the respective listings.

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 a value exceeding the cut-off value with one unit
- '≤x' or '≥x': imputation by x.

This also applies to normal limits expressed as such.

No such imputations will be done for urinalysis parameters as these are usually character/categorical expressions

6.2.2. Analysis Methods

Laboratory data will be summarized by type of laboratory test. Actual values and changes from baseline will be summarized by treatment group at each scheduled time point.

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

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

A listing of abnormal individual subject hematology and clinical chemistry values from scheduled and unscheduled time points will be provided. This listing will include all other time points for the corresponding subject/parameter. Grade 2 or higher toxicity laboratory values will be listed separately. Urinalysis results will be listed.

6.3. Vital Signs and Physical Examination Findings

Systolic and Diastolic blood pressure, heart rate, respiratory rate, body temperature and oxygen saturation ($SpO_{2)}$ will be investigated.

6.3.1. Definitions

The vital signs abnormalities will be defined as indicated in Table 12. In determining the abnormalities, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period for each trial phase separately, including post-baseline scheduled and unscheduled measurements of that phase.
- The abnormalities ‘abnormally low’ and ‘abnormally high’/grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high or graded value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

Table 12: Clinically Important Abnormalities in Vital Signs

Vital Sign	Abnormality Code	Criteria
Systolic blood pressure	Abnormally low	≤ 90 mmHg
	Grade 1 or mild	> 140 mmHg - < 160 mmHg
	Grade 2 or moderate	≥ 160 mmHg - < 180 mmHg
	Grade 3 or severe	≥ 180 mmHg
Diastolic blood pressure	Abnormally low	≤ 50 mmHg
	Grade 1 or mild	> 90 mmHg - < 100 mmHg
	Grade 2 or moderate	≥ 100 mmHg - < 110 mmHg
	Grade 3 or severe	≥ 110 mmHg
Respiratory rate	Grade 1 or mild	17-20 breaths per minute
	Grade 2 or moderate	21-25 breaths per minute
	Grade 3 or severe	> 25 breaths per minute
	Grade 4 or potentially life threatening	Intubation
Oxygen Saturation	Abnormally low	< 95%
Temperature (oral)	Abnormally high	> 38.0 ^{o}C
Pulse/Heart Rate	Abnormally low	≤ 45 bpm
	Abnormally high	≥ 120 bpm

Emergent definition for abnormalities

An abnormality will be considered emergent if it is worse than baseline. If baseline is missing, the abnormality is always considered emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also emergent.

6.3.2. Analysis Methods

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

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

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

A listing of abnormal (or grade 2 or higher) individual subject vital signs values will be provided. This listing will include all other time points for the corresponding subject/parameter.

6.4. Electrocardiogram

PR, QT, QRS, QTc intervals and heart rate will be investigated. QTcB and QTcF values will be used as reported by the central ECG provider, they will not be recalculated.

6.4.1. Definitions

The ECG abnormalities will be defined as indicated in Table 13. In determining the abnormalities, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period and for each trial phase separately, including post-baseline scheduled and unscheduled measurements of that phase.
- The abnormalities 'abnormally low' and 'abnormally high'/grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high or graded value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%).

Table 13: ECG Abnormalities

ECG parameter	Abnormality Code	Criteria
Abnormalities on actual values		
Pulse/Heart Rate	Abnormally low	≤ 45 bpm
	Abnormally high	≥ 120 bpm
PR	Abnormally high	≥ 210 ms
QRS	Abnormally high	≥ 120 ms
$QT_{corrected}$	Borderline prolonged QT	450 ms < QTc ≤ 480 ms
	Prolonged QT	480 ms < QTc ≤ 500 ms
	Pathologically prolonged QT	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)		
$QT_{corrected}$	Normal QTc change	ΔQTc < 30 ms
	Borderline QTc change	30 ms ≤ ΔQTc ≤ 60 ms
	Abnormally high QTc change	ΔQTc > 60 ms

Emergent definition for abnormalities

An abnormality will be considered emergent if it is worse than baseline. If baseline is missing, the abnormality is always considered as emergent. A shift from 'abnormally low' at baseline to 'abnormally high' or 'grade …' post baseline (or vice versa) is also emergent.

Triplicate ECG assessments

For time points on which triplicate ECGs apply (expected for all time points), a mean value per triplet cluster, will be calculated per time point before any further handling. This mean value will be used through the entire analysis. In the analysis dataset, the time of the first triplet member will be retained for this average record.

Rounding

When ECG parameters need to be derived or any operations should be performed (e.g. averaging over many assessments/triplicates), no rounding to the integer/unit will be performed; the maximum stored resolution of these vales in the derived dataset(s) will be limited to 8 decimal positions. When used in tables, these values will be presented using formats reflecting the resolution of the unit applicable to the respective parameter (milliseconds, beats per minute).

6.4.2. Analysis Methods

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

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

A tabulation of the worst QT/QTc change versus baseline per treatment per phase (treatment phase, follow-up phase) and for the combination of treatment and follow-up phase will be presented

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

A listing of abnormal individual subject ECG values will be provided. This listing will include all other time points for the corresponding subject/parameter.

7. HEALTH ECONOMICS

7.1. Definitions

Medical Resource Utilization will be assessed by the number and duration of medical care encounters for RSV infection or complications associated with RSV per investigator assessment.

Information will be provided as:

- Number of medical encounters and rationale (AE, Other)
- Type of encounter such as medical practitioner office, emergency room, hospitalization, intensive care unit, palliative care unit among others
- Specialist involved
- Frequency of visits.

7.2. Analysis Methods

The proportion of subjects requiring any medical encounter will be shown in a frequency tabulation by treatment group with the corresponding 90% confidence interval (exact Clopper-Pearson method).

Similar frequency tables will be provided for type of medical encounter. Data will also be summarized stratifying by presence of any comorbidity.

Additional information on medical encounters (frequency of visits, type of practitioner) will be listed.

8. VIROLOGY

The sequencing results of the F-gene (and other regions of the RSV genome at the request of the protocol virologist) and changes from baseline will be summarized. Sequencing results may be presented in a separate report.

8.1. Definitions

Viral Strain Typing

The RSV subtype is determined at baseline using the RSV-A/B RT-qPCR assay performed in the central lab.

Viral Sequencing

Viral resistance will be evaluated by next-generation sequencing (NGS) of the RSV Fusion (F) gene using a read frequency cut-off that will be defined in the Data Presentation Sheet.

Baseline samples from all subjects will be sequenced to identify pre-existing polymorphisms in the F gene. Post-baseline sequencing will be performed on the last evaluable on-treatment sample and/or during follow-up for all subjects (if viral load is high enough) to identify emerging amino acid substitutions in the F gene. Additional post-baseline sequencing can be performed on request of the sponsor virologist.

Genetic variations

Genetic variations are defined as changes (on amino acid or nucleotide level) in the subject's virus's sequence compared to a reference sequence. Genetic variations can include substitutions, insertions and deletions. The reference sequences used will be RSV-A Long strain (GenBank Accession number AY911262) for RSV-A samples and RSV-B strain 9320 (GenBank Accession number AY353550) for RSV-B samples. Genetic variations will be reported on amino acid level.

- **Baseline polymorphism**: amino acid difference from the RSV-A or RSV-B reference strain detected at baseline above a certain NGS read frequency cut-off, which is to be defined.
- **Emerging genetic variation:** a genetic variation (amino acid substitution, insertion or deletion) that is absent (i.e. below a to be defined NGS read frequency cut-off) at baseline but present above a certain to be defined NGS read frequency cut-off at a later post-baseline time point.
- **Enriched genetic variation**: a genetic variation (amino acid substitution, insertion or deletion) that is present at baseline with an NGS read frequency cut-off that will be defined and detected post-baseline with an increase in NGS read frequency compared to baseline.

The minimum increase in NGS read frequency to meet the definition of enriched genetic variation will be defined.

- **Genetic variation profile**: a specific genetic variation or combination of genetic variations at one or more time points.
- **RSV F-gene amino acid positions of interest**:
    - Short list of 8 F-gene positions of interest for JNJ-53718678, based on in vitro selection experiments with JNJ-53718678 and/or in vitro reduced susceptibility to JNJ-53718678: positions 141, 143, 394, 398, 400, 486, 488, and 489.
    - Long list of 20 F-gene positions of interest for the class of RSV fusion inhibitors, based on in vitro selection experiments, clinical observations, and/or in vitro reduced susceptibility to RSV fusion inhibitors: positions 127, 138, 140, 141, 143, 144, 323, 338, 392, 394, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517.

The read frequency cut-off that will be used for reporting RSV F-gene NGS data, as well as the read frequency cut-offs used in the definitions of baseline polymorphisms, emerging and enriched genetic variations will be defined in the Data Presentation Specifications.

Analysis Time Points

Virology results will be assigned to the visit windows as described in Sections 2.1.2 Phase Definitions and 2.1.4 Visit Windows. In addition to the time points corresponding to the visits at which samples for RSV F gene sequencing are collected, the below time points will be considered:

- Baseline (BL): Time point with sequencing data available closest prior to the first dose. This will be the Day 1 pre-treatment sample; however, if RSV F gene sequencing data cannot be obtained from this sample, the screening sample may be used for sequencing.
- Last Evaluable On-Treatment Time Point: Last available post-baseline time point during the treatment phase with sequencing data available. In case no On-Treatment assessment is available, the first assessment during Follow-Up is selected instead.
- Time Point of Sequence during the Follow-Up phase: Last available post-baseline time point during the follow-up phase with sequencing data available.
- Entire post-baseline phase: Aggregate of all available post-baseline time points in the study with sequencing data available

8.2. Analysis Methods

8.2.1. Viral Strain Typing

The number of subjects by RSV subtype will be tabulated in frequency outputs (n, %).

8.2.2. Viral Sequencing

Baseline

The prevalence of baseline polymorphisms in the RSV F-gene, ie the number of subjects with baseline polymorphisms in the RSV F-gene, will be tabulated in frequency outputs (n, %).

Amino acid changes from reference sequence at baseline will be listed for all subjects using a defined NGS read frequency cut-off (will be defined in the Data Presentation Specifications).

Post-baseline

Emerging and enriched genetic variations will be tabulated by analysis time point in frequency outputs (n, %). Amino acid changes from reference sequence will be listed for all subjects with post-baseline sequencing data using a defined NGS read frequency cut-off (will be defined in the Data Presentation Specifications).

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ATTACHMENTS

Attachment [1]: Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table – November 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

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	**Life-threatening** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization [WHO]) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- 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.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
Absolute Neutrophil Count	1,000-1,500/ mm^3	750-999/ mm^3	500-749/ mm^3	<500/ mm^3
Platelets	75,000-99,999/ mm^3	50,000-74,999/ mm^3	20,000-49,999/ mm^3	<20,000/ mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 / mm^3	15,000-30,000/ mm^3	>30,000 or <1,000 / mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ mL	41-50 mcg/ mL	51-60 mcg/ mL	> 60 mcg/ mL
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* 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 therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, 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 abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* 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 abnormal calcium *with* life-threatening arrhythmia or tetany

CHEMISTRIES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* 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 therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	>6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR RBC casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG 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				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV1 25% - 50% of peak flow; or retractions present	cyanosis: FEV1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink flu ids; requires IV fluids

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, eg, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, eg, vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELATEL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15mm	15-30 mm	>30mm	
Erythema	<15mm	15-30 mm	>30mm	
Edema	<15mm	15-30 mm	>30mm	
Rash at Injection Site	<15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	>40 C or >105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self

Attachment [2]: Inclusion/exclusion criteria

Inclusion Criteria

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

1. Male or female.

2. ≥18 years of age.

3. Must sign an ICF indicating they understand the purpose of, and procedures required for, the study and is willing to participate in the study.

   Note: Prior to signing the main consent form for the study, subjects may specifically allow for the collection and testing of nasal mid-turbinate swabs by signing the pre-screening (diagnostic) ICF.

4. Subjects must have an acute respiratory illness with signs and symptoms consistent with a viral infection (eg, fever, cough, nasal congestion, runny nose, sore throat, myalgia, lethargy, shortness of breath, or wheezing) with onset ≤5 days from the anticipated time of randomization. Onset of symptoms is defined as the time the subject becomes aware of the first sign and/or symptom consistent with a viral infection. Efforts should be made to determine the time of onset of symptoms as accurately as possible (in relation to routine daily activities).

   Note: The viral infection may present in any way as long as the underlying precipitant of the illness is considered by the investigator to be due to RSV infection. Examples of such an illness include:

   - An upper or lower viral respiratory tract infection (eg, "flu-like illness");
   - Pneumonia;
   - Respiratory distress;
   - Asthma exacerbation;
   - COPD exacerbation.

5. Subject has been diagnosed with RSV infection using a rapid PCR-based (preferably locally available) or rapid-antigen-detection test.

   Note: If a patient has a positive similar diagnostic test from another study and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility.

6. Before randomization, a woman must be not of childbearing potential defined as:

   - Premenarchal
     A premenarchal state is one in which menarche has not yet occurred.

- Postmenopausal
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. An available high follicle-stimulating hormone level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.
- Permanently sterile
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

7. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 30 days after the last dose of study drug.

8. All women must have a negative urine β-human chorionic gonadotropin pregnancy test at screening.

9. A male subject must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male subjects should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak.

   Note: Contraceptive (birth control) use by subjects should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

10. A male subject must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose of study drug.

11. Willing and able to adhere to the lifestyle restrictions specified in this protocol (please see protocol Section 4.3).

12. With the exception of the RSV-related illness the subject must be medically stable on the basis of physical examination, medical history, vital signs, and ECG performed at screening. If there are abnormalities, they must be consistent with the underlying condition (RSV disease and/or comorbid condition) in the study population as evaluated by the investigator (with exception of QTcF interval >500 ms, see exclusion criterion 13). This determination must be recorded in the subject's source documents and initialed by the investigator.

Exclusion Criteria

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

1. Hospitalized subjects or subjects expected to be hospitalized within 24 hours of screening.

   Note: Any stay in the emergency room or in the observational unit of at least 24 hours will be considered hospitalization for the purposes of the study.

2. History of or concurrent illness (beyond a comorbid condition) that in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject or that could prevent, limit, or confound the protocol-specified assessments.

3. Subjects who had major surgery within the 28 days prior to randomization or have planned major surgery through the course of the study.

4. Subjects who are considered by the investigator to be immunocompromised within the past 12 months, whether due to underlying medical condition (eg, malignancy or genetic disorder other than immunoglobulin A deficiency, or human immunodeficiency virus [HIV] infection) or medical therapy (eg, medications other than corticosteroids for the treatment of COPD or asthma exacerbations, chemotherapy, radiation, stem cell or solid organ transplant).

5. Subject has known or suspected chronic or acute hepatitis B or C infection.

6. Subject has known allergies, hypersensitivity, or intolerance to JNJ-53718678 or to any of the excipients of the JNJ-53718678 or placebo formulation (refer to the IB).

7. Subject with current or planned participation in another clinical study where study drug/investigational device is being administered while participating in the current study.

8. Subjects unwilling to undergo mid-turbinate nasal swab procedures or with any physical abnormality which limits the ability to collect regular nasal specimens.

9. Subjects unable to take medications orally or with a known gastrointestinal-related condition that is considered by the sponsor or investigator to be likely to interfere with study drug ingestion or absorption.

10. Women who are pregnant or breastfeeding.

11. Men who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.

12. Subject with clinically significant abnormal ECG findings (other than QTcF interval >500 ms, see exclusion criterion 13) not consistent with the underlying condition in the study population, as judged by the investigator.

13. Confirmed QTcF interval >500 ms per the machine read parameter result at screening. Confirmation needs to be obtained by repeat triplicate ECG recording prior to dosing.

14. Subjects who are using any disallowed medication as listed in Section 8 of the protocol.

15. Subjects with history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5^{th} edition) criteria within 1 year before screening.

16. Subjects who received an investigational drug, an investigational vaccine, or used an invasive investigational medical device within 30 days or 5 elimination half-lives (whichever is longer) before the planned first dose of study drug or is currently enrolled in an investigational study.

17. Subject is a family member of the employees of the investigator or study-site with direct involvement in the proposed study or other studies under the direction of that investigator or study-site or of the investigator.

Attachment [3]:
Respiratory infection-patient reported outcomes (ri-pro ©) symptom questionnaire

Domain	Items	Scoring and Minimum Data Requirement
Nose	Runny or dripping nose Congested or stuffy nose Sneezing Sinus pressure	Arithmetic mean of 4 items Daily score for 3 of 4 items must be present to calculate domain score
Throat	Scratchy or itchy throat Sore or painful throat Difficulty swallowing	Arithmetic mean of 3 items Daily score for 2 of 3 items must be present to calculate domain score
Eyes	Teary or watery eyes Sore or painful eyes Eyes sensitive to light	Arithmetic mean of 3 items Daily score for 2 of 3 items must be present to calculate domain score
Chest/Respiratory	Trouble breathing Chest congestion Chest tightness Dry or hacking cough Wet or loose cough Coughing Coughed up mucus or phlegm	Arithmetic mean of 7 items Daily score for 5 of 7 items must be present to calculate domain score
Gastrointestinal	Felt nauseous Stomach ache Vomit (frequency) Diarrhea (frequency)	Arithmetic mean of 4 items Daily score for 3 of 4 items must be present to calculate domain score
Body/Systemic	Felt dizzy Head congestion Headache Lack of appetite Sleeping more than usual Body aches or pains	Arithmetic mean of 11 items Daily score for 8 of 11 items must be present to calculate domain score

Domain	Items	Scoring and Minimum Data Requirement
	Weak or tired Chills or shivering Felt cold Felt hot Sweating	

Adult RSV additional questions

Additional Questions About Health and Functioning	
1. Did you take any medicine for our respiratory infection symptoms today?	Yes
	No
2. Did you use any rescue medicine today for asthma or COPD?	I do not take medicine for asthma or COPD
	Yes
	No
3. Since this time yesterday, how much of the time did you breathe oxygen from an oxygen tank?	None of the time
	Less than an hour
	1 to 4 hours
	More than 4 hours
4. Overall, how severe were your respiratory infection symptoms today?	No respiratory infection symptoms today
	Mild
	Moderate
	Severe
	Very Severe
5. Overall, how were your respiratory infection symptoms today compared to yesterday?	Much better
	Somewhat better
	A little better
	About the same
	A little worse
	Somewhat worse
	Much worse
6. How much did your respiratory infection symptoms interfere with your usual activities?	Not at all
	A little bit
	Somewhat
	Quite a bit
	Very Much

7. Have you returned to your usual activities today?	Yes
	No
8. In general, how would you rate your physical health today?	Excellent
	Very good
	Good
	Fair
	Poor
9. Have you returned to your usual health today?	Yes
	No

Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)

Please read each of the following questions and select the answer thinking about when you felt the worst in the past **12/24 hours**.

1. During the past 12/24 hours, have you had the following symptoms?

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Wheezing	☐	☐	☐	☐
k. Coughing up phlegm (sputum)	☐	☐	☐	☐
l. Short of breath	☐	☐	☐	☐
m. Loss of appetite	☐	☐	☐	☐

2. During the past 12/24 hours, how able were you to:

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

3. During the past 12/24 hours, have you felt:

	Not at all	**Somewhat**	**Moderately**	**Extremely**
a. Irritable	☐	☐	☐	☐
b. Helpless	☐	☐	☐	☐
c. Worried	☐	☐	☐	☐
d. Frustrated	☐	☐	☐	☐

4. During the past 12/24 hours, have you been concerned about:

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

Attachment [4]: EQ-5D-5L

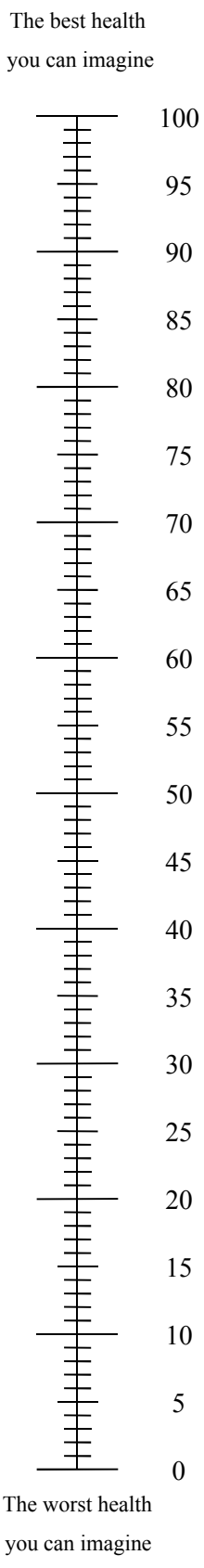
EQ-5D-5L Dimensions

Dimension		Level		Interpretation
1	Mobility	1	No problems	I have no problems walking
		2	Slight problems	I have slight problems walking
		3	Moderate problems	I have moderate problems walking
		4	Severe problems	I have severe problems walking
		5	Extreme problems	I am unable to walk
2	Self-care	1	No problems	I have no problems washing or dressing myself
		2	Slight problems	I have slight problems washing or dressing myself
		3	Moderate problems	I have moderate problems washing or dressing myself
		4	Severe problems	I have severe problems washing or dressing myself
		5	Extreme problems	I am unable to wash or dress myself
3	Usual activities	1	No problems	I have no problems doing my usual activities
		2	Slight problems	I have slight problems doing my usual activities
		3	Moderate problems	I have moderate problems doing my usual activities
		4	Severe problems	I have severe problems doing my usual activities
		5	Extreme problems	I am unable to do my usual activities
4	Pain/discomfort	1	No problems	I have no pain or discomfort
		2	Slight problems	I have slight pain or discomfort
		3	Moderate problems	I have moderate pain or discomfort
		4	Severe problems	I have severe pain or discomfort
		5	Extreme problems	I have extreme pain or discomfort
5	Anxiety/depression	1	No problems	I am not anxious or depressed
		2	Slight problems	I am slightly anxious or depressed
		3	Moderate problems	I am moderately anxious or depressed
		4	Severe problems	I am severely anxious or depressed
		5	Extreme problems	I am extremely anxious or depressed

EQ-5D-5L VAS

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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
12235	0,176	12424	0,35	13113	0,744	13252	0,075

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
13441	0,371	14125	0,185	14314	0,435	14453	0,007
13442	0,315	14131	0,6	14315	0,247	14454	-0,074

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

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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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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
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		

Health state	Index Value	Health state	Index Value	Health state	Index Value	Health state	Index Value
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				