**Janssen Research & Development**

# Statistical Analysis Plan
# Amendment 3

## A Phase 2, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Relationships of Different Doses of JNJ-53718678 in Children ≥28 Days and ≤3 Years of Age With Acute Respiratory Tract Infection Due to Respiratory Syncytial Virus Infection

**Protocol 53718678RSV2002; Phase 2**

**JNJ-53718678**

**Status:** Approved
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**Prepared by:** Janssen Research & Development, a Division of Janssen Pharmaceutica NV.
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**Compliance:** The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

# TABLE OF CONTENTS

# LIST OF IN-TEXT TABLES AND FIGURES

## TABLES



## FIGURES

## AMENDMENT HISTORY

| Version | Effective Date | Description of Changes |
|---|---|---|
| Final version | 07DEC2018 | |
| Amendment 1 | 08OCT2019 | General clarifications added for:<br>• Section 2.1.1 Phase Definitions: definition of the screening phase considering the diagnostic ICF is required in some countries as testing for RSV is not part of Standard Of Care (SOC).<br>• Section 2.1.2 Baseline: for Viral Load (VL) a sample taken at the same date and time of dosing can be considered.<br>• Section 2.1.4 Analysis Windows for Analysis Visits and Time Points: further details on how to handle Table 5 Visit Windows for PRESORS ClinRO, PRESORS ObsRO, Clinical Evaluation (including SBP/DBP) and Body Temperature and Table 6 Worst per Day, secondary selection provided as footnote.<br>• Section 3 Interim Analysis and Data Monitoring Committee Review: more details added on the endpoints to be provided for each interim analysis.<br>• Section 4.1 Demographics and Baseline: the frequency table of mismatches for the stratification factors was added for completeness.<br>• Section 5.1 Analysis Specifications: clarified that derived stratification factors based on eCRF data will be used in the analyses when randomization stratification factors referred in the model.<br>• Section 5.2.3 Analysis Methods: the following clarifications were added.<br>o the numeric dose levels to be used in MCP-mod.<br>o for subgroup analysis the model will include the subgroup variable as covariate, subgroup-by- treatment, subgroup-by-visit and subgroup-by-visit-by-treatment interactions.<br>• Section 5.3.1.1 RSV RNA Viral Load: clarification on the calculation of the viral load of AUC with missing data added. Imputation by carrying last observation forward will only be done for a maximum time period of 24 hours<br>• Section 5.3.1.2 Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): additional clarifications in Table17 were provided:<br>o Score 0-3, the higher the score the worse the symptom/concept.<br>o for the worst score for the daily summary score.<br>o Time to event is defined as time to the first occurrence of the event.<br>• Section 5.3.2.1 RSV RNA Viral Load (qRT-PCR): clarified that: |

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| | | ○ for subgroup analysis the model will include the subgroup variable as covariate, subgroup-by- treatment, subgroup-by-visit and subgroup-by-visit-by-treatment interactions.<br>○ the comparison of proportions will be carried out using the Cochran Mantel Haenszel test adjusted for each stratification factor separately.<br>○ for time to virus undetectable, estimates and covariances from AFT model will be used in MCP-mod analysis.<br>• Section 5.3.2.2 Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): clarified that<br>○ the restricted maximum likelihood based repeated measures model will be performed for each instrument concept, maximum summary scores and daily summary scores.<br>○ for time to different resolutions, estimates and covariances from AFT model will be used in MCP-mod analysis.<br>• Section 5.3.2.3.1 Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature: further details on how to identify the worst value per day over 24h were provided.<br>• Section 5.3.2.3.2 Hospitalized subjects only: for time to different resolutions, estimates and covariances from AFT model will be used in MCP-mod analysis.<br>• Section 5.6 Decision Rules at Interim Analyses. A figure describing the decision rules for futility, based on different endpoints was added.<br>• Clinical Laboratory Section 6.2.1 Definitions: not all parameters have toxicity grades defined for all age groups. Available grading as provided by the central laboratory will be used in the analysis.<br>• ECGs Section 6.4.1 Definitions: abnormal changes from baseline were missing in Table 27 and have been added.<br>• Attachment 2 PRESORS ObsRO Scoring System: clarified derivation of concept scores when a question contains information for different concepts.<br>• Attachment 3 PRESORS ClinRO Scoring System: clarified derivation of concept scores when a question contains information for different concepts and/or is assessed at different recall time (e.g. past 12h, now)<br><br>Following corrections were made:<br>• Section 1.4 Sample Size Justification: protocol stated 1-sided alpha of 2.5% which is equivalent to 2-sided alpha of 5%; so for consistency the same expression is used as in the protocol.<br>• Section 2.1.4 Analysis Windows for Analysis Visits and Time Points: In Table 5 correction was done for time interval 228h (Day 10.5) and 240h (Day 11) |

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| | | where instead of 231h it should be 233h and 234h respectively.<br>• Section 5.3.2.2: Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): the following corrections were done<br>  o in the restricted maximum likelihood based repeated measures model:<br>  ▪ Baseline score has been added to the model as a covariate.<br>  ▪ Model modification based on covariate significant level has been removed because not applicable to the repeated measures model.<br>  o for status of RSV symptoms, status of health, status of improvements of RSV symptoms and status return to pre-RSV disease health (ObsRO), differences in proportions will be compared by using CMH instead of Wilson test.<br>•<br>• : the following corrections were done:<br>  o Scores for breathing problems as “nostril flaring” and “head bobbed back and forth when breathing” are considered severe (score =3) instead of moderate (score =2).<br>  o Word “worst” was removed from the general instructions on how to derive the summary scores.<br>• Attachment 3: PRESORS CLINRO Scoring System: word “worst” was removed from the general instructions on how to derive the summary scores.<br><br>Additional information/analysis:<br>• Section 2.3.2.2 Per Protocol Set: Missing PRESORS ObsRO at baseline is considered as major protocol deviation.<br>• Section 5.2.3 Analysis Method: the following text has been added<br>  o for the restricted maximum likelihood based repeated measures model, an unstructured (co)variance structure is used to model the within-subject errors.<br>  o a sensitivity analysis for the primary endpoint considering randomization stratification factors as per IWRS instead of the derived randomization stratification factor.<br>• Section 5.3.1.2 Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): added the time to improvement of RSV symptoms (ObsRO) variable.<br>• Section 5.3.1.3.2. Hospitalized Subjects Only: added the time to resolution of RSV other symptoms (ClinRO) |

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| | | • Section 5.3.2.1 RSV RNA Viral Load (qRT-PCR): for time to virus undetectable the following has been added:<br>o stratified Cox proportional hazard model to produce survival curves by stratification factors has been added.<br>o Similar Cox model including the subgroup variable and its interaction with treatment for subgroup analysis<br>o A forest plot for subgroups Hazard Ratios (HR) will be presented will be presented.<br>• Section 5.3.2.2 Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): the following evaluations and analyses have been added:<br>o Summary table of the reasons for missing PRESORS (ObsRO and ClinRO).<br>o Summary overview of the number of caregivers per subject.<br>o Graphical evaluation of the two different ways to define the worst score for the daily summary score.<br>o sensitivity analyses added for the time to resolution of all RSV symptoms (ObsRO) endpoint considering different imputation methods.<br>o For different time to the "events" variables:<br>▪ the stratified Cox proportional hazard model to produce survival curves by stratification factors has been added.<br>▪ Similar Cox model including the subgroup variable and its interaction with treatment for subgroup analysis<br>▪ Forest plot for subgroups HRs<br>o time to improvement and time to resolution RSV other symptoms analyses have been added.<br>• Section 5.3.2.3.2 Hospitalized Subjects Only: for the different time to "events" variables, the following analyses have been added<br>o stratified Cox proportional hazard model to produce survival curves by stratification factors has been added.<br>o Similar Cox model including the subgroup variable and its interaction with treatment for subgroup analysis<br>o Forest plot for subgroups HRs.<br>• Section 5.5 Correlation Between Antiviral Effect and Clinical Course Endpoint: a plot of viral load versus daily summary key RSV symptom severity score over time has been added.<br>Updates as per CTPA#1 approved 14MAY2019: |

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| | | • Section 1.2 Trial Design: increased sample size for Cohort 1 72 to approximately 144 subjects. Figure 1 replaced with numbers updated accordingly<br>• Section 1.4 Sample Size Justification:<br>  o Rationale and calculations for the increased sample size in Cohort 1 was provided.<br>  o Number of subjects from each cohort to be included in the clinical course analyses was updated.<br>  o Clarified that only the information from Cohort 2 will be used in the sample size re-estimation.<br>• Section 3 Interim Analysis and Data Monitoring Committee Overview:<br>  o clarified that each Interim Analysis (IA) will be preferably performed at the end of the hemispheric season.<br>  o for IA#2 added that approximately between 70-80 subjects from Cohort 1 will be included in the analysis.<br>  o for IA#3 clarified that data from both cohorts will considered for analyses of antiviral activity and that only Cohort 2 data will be used for sample size re-estimation.<br>  o Figure 2 replaced with updated numbers as per changes in the sample size.<br>• Section 5.1 Analysis specifications: clarified that analyses will be performed both by combining information from both cohorts and by cohort separately.<br>• Section 5.1.1 Level of Significance: added that for clinical course endpoints, both the unadjusted and the multiplicity adjusted p-value will be provided.<br>• Section 5.2.3.1 Methods to Control Type I Error for Multiplicity and Adaptations has been added.<br>• Section 5.6 Decision Rules at Interim Analyses: added that for IA#3 & IA#4 the analysis will be performed with all data available from both cohorts and a second time with balanced cohorts. Details on how to proceed in case of inconsistencies in results were included.<br>• Clinical Laboratory Section 6.2.1 Definitions: note added since coagulation will not be analyzed in subjects enrolled under this protocol amendment.<br><br>Updates as per CTPA#2 approved 05JUL2019:<br>• Section 1.2 Trial Design: clarified that number of subjects with symptom onset ≤ 3 days must be a minimum of 45 % of all enrolled subjects in Cohorts 1 and 2 (i.e. maximum 55% of subjects could be enrolled in the >3 days stratum).<br>• Section 1.5 Randomization and Unblinding: subjects with symptoms onset ≤ 3 days must be a minimum of 45 % of all enrolled subjects. |

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| | | • Section 5.6 Decision Rules at Interim Analyses: clarified that balanced cohorts will also be considered in case of severe imbalance between <=3 days and >3-5 days symptom onset strata. |
| Amendment 2 | 10JUL2020 | Following clarifications made:<br>• Amendment History, version section format changed to clearly provide amendment identifier rather than version number.<br>• In Section 2.3.2.2 Per Protocol Set since subjects who early discontinued study medication will be considered within the criterion "Subject missed more than one dose of study drug".<br>• Section 5.3.2.2 Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS): a full description of the analysis model has been included to clarify that baseline viral load will not be included in the model, but continuous covariates will be included for both baseline score and analysis visit -by-baseline score.<br>• Section 5.6 Decision Rules at Interim Analyses:<br>o Clarification that a balanced analysis should only be carried out in the situation that there is severe imbalance ( i.e. : >55% subjects in symptoms onset >3-5 days ) between the <=3 days and >3 days since symptom onset stratum AND where are more subjects in the >3-5 day stratum than in the <=3 days stratum.<br>o Clarification that the conditional power for viral load endpoint at IA#3 should be based on combined data from Cohort 1 and 2.<br>o Clarification that the conditional power for clinical course endpoints at IA#3 should be based on Cohort 2 only.<br><br>Following corrections were made:<br>• Exploratory endpoint "Respiratory infection complication" relabeled as "RSV-related complication" to avoid misunderstandings since one of the subcategories is already respiratory complication. Corrections done :<br>o Section 3 Interim Analysis and Data Monitoring Committee<br>o Section 5.4.1 Definition in Table 19<br>o Section 5.4.2 Analysis Methods<br>o Section 5.5 Correlation between Antiviral Effect and Clinical Course<br><br>Additional information/analyses:<br>• Due to PRESORS validation results available, PRESORS analyses will additionally be based on the modified scores and resolution definition for:<br>o ObsRO concepts: Dehydration, Retractions, Cyanosis and Apnea. |

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| | | ○ ClinRO concepts: Retractions, Cyanosis and Apnea<br>○ Exclusion of Cyanosis and Apnea from the derivations of the parameters Overall Symptoms, Key RSV Symptoms, Respiratory Symptoms and General Illness behavior.<br>A new Section 5.3.1.2.1 PRESORS adapted Definitions has been created providing detailed information and Table 15 as well as Attachments 2 &3, have been updated accordingly.<br>• A modified definition of the RSV-related complication has been added in the Section 5.4.1 Exploratory Endpoints, Table 19 The RSV-Related Complications modified definition has 4 complication categories ( respiratory, infectious, cardiovascular and acid-base or electrolyte) instead of the 3 complication categories (respiratory, non-respiratory and other) as in the original definition.<br>• Section 5.6 Decision Rules at Interim Analyses, Table 20:<br>○ The endpoint, 'Time to resolution of all RSV symptoms (ObsRO)' has been updated to 'Time to resolution of key RSV symptoms (ObsRO)'.<br>○ The endpoint 'Overall RSV severity score (ObsRO) at Day 8' has been updated to 'Change from baseline in key RSV severity score (ObsRO) at Day 8'.<br>○ The endpoint 'Incidence of Respiratory Infection Complication' has been updated to 'Incidence of RSV-related Complication' to reflect the updated definition for this endpoint.<br>○ The Target Value for 'Change from baseline in key RSV severity score (ObsRO) at Day 8' has been updated to represent a 20% effect on the change from baseline rather than a 20% effect on the absolute score.<br>• Section 5.6 Decision Rules at Interim Analyses; Interim Analysis 3: Additional information has been added to describe the calculations of conditional power for viral load endpoint and the three key clinical course endpoints. |
| Amendment 3 | 20 May 2021 | Updates included as per CTPA#4 approved 26 May 2020:<br>• Section 1.2 Trial Design: described change in dosing regimen from QD to BID and subsequent handling in analyses: treatment groups will be analyzed and presented regardless of dosing regimen (QD or BID).<br>• Section 2.1.4 Analysis Windows for Analysis Visits and Time Points: added that ECG assessments are to be collected around 1h post-dose on Study Day 1 and Study Day 3. On these days, a time window of 45 min to 90 min will additionally be applied after assigning the target day |

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| | | • Section 6.2.1 Definitions: included reference to levels of potassium and magnesium to be determined by the central laboratory. In case of hypokalemia or hypomagnesemia, the levels of potassium and magnesium are to be monitored locally and corrected to prevent cardiac disturbances. Data will be listed.<br><br>Updates included as per CTPA#6 approved 01 December 2020:<br>• Section 2.4 Subgroups:<br>o Cohort (Class 2) defined given change to inclusion criterion 4 aimed at maximizing enrollment of subjects with at least moderate RSV disease severity.<br>o Specified that in case of population enrichment decision (subjects with symptom onset ≤3 days before randomization), efficacy analyses will focus on those subjects with symptom onset ≤3 days before randomization stratum only.<br><br>Following notable clarifications and corrections were made:<br>• Applicable revisions/clarifications through various sections:<br>o Added use of 'analysis' to phase (treatment and/or follow-up) to differentiate between analysis definition and protocol-defined study phases.<br>o Clarified throughout to state that the MCP-Mod test for trend in viral load will use a 1-sided 2.5% Type I error rate.<br>• Section 2.1.2 Baseline: baseline derivation for ECG triplicate assessments clarified.<br>• Section 2.1.4 Analysis Windows for Analysis Visits and Time Points: removed reference to data handling, if for a given window both, on-site assessment and home-based assessment are available for nasal swab collection (for viral load). Sample setting of collection is not considered for the analysis.<br>• Section 2.3.3.1 Safety Set: corrected 'analyzed as treated' definition to consider active vs placebo in addition to dose level.<br>• Section 2.4 Subgroups: revised data handling, subgroups and their classifications given development of subgroups through completion of previous IAs, in addition to further development of other studies in the program. Section has been revised to facilitate cross-reference through subsequent sections in such a way that any future changes to subgroup analyses will not necessarily require extensive SAP updates.<br>• Section 4.3 Treatment Compliance: derivations have been expanded given the change from QD to BID dosing regimen with added clarity regards the derivation of % compliance and subsequent categorization.<br>• Section 4.5 Medical History: added tabulation of general medical history. |

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| | | • Section 4.6 Prior and Concomitant Medications: added medications of interest, aligned with study RSV3001, to assess the use of these medications of special interest and their potential impact on the PRESORS assessments.<br>• Section 5.2.3 Analysis Method: added sensitivity analysis excluding nasal swab samples identified as:<br>o Ribonuclease P (RNAse P [housekeeping gene]): result = Target Not Detected AND<br>o RSV A: result = Target Not Detected AND<br>o RSV B: result = Target Not Detected<br>• Section 5.3.1.1 RSV RNA Viral Load, 5.3.1.2 PRESORS, 5.3.1.3 Other Clinical Course Parameters<br>o Added definitions, derivations and tabulation of missing data PRESORS ObsRO/ClinRO.<br>o Added tabulation of number of caregivers/investigators.<br>• Section 5.3.1.3.2 Hospitalized Subjects only:<br>o Revised time (hours) to end of supplementation (oxygen and/or feeding/hydration) to include up to 72h from first hospital discharge specification. Definition was revised, based on previous IAs, to ensure accurate derivation of resolution per subject and not one confounded by continued use of supplementation.<br>o Clarified that normalization of vital signs (HR and RR) is based on investigator evaluation only.<br>o Added definition, derivations and tabulation of re-hospitalization.<br>• Section 5.3.2 Endpoint-specific Analysis Methods:<br>o Streamlined time to event analysis by removing all references to COX proportional analysis model as the same information can be obtained from the AFT analyses.<br>o Updated AFT model to exclude baseline $\log_{10}$ RSV RNA viral load as covariate for clinical course endpoints.<br>o Expanded methodology for association between key endpoints and baseline indicators of interest<br>o Revised methodology for comparing proportions accounting for the randomization stratification factors.<br>• Section 5.4: Exploratory Endpoints: the exploratory efficacy endpoints listed in Section 5.4 have additionally been included, based on previous IAs with new information becoming available during the course of the study. These additional exploratory efficacy endpoints support decision-making for further development of JNJ-53718678 and interactions with health authorities.<br>• Section 5.6 Decision Rules at Interim Analyses: the calculation of conditional power for the change from baseline in key RSV symptoms at Day 8 was corrected to account for the correlation between $Z_{TV}$, the test statistic to test the null |

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| | | hypothesis that the difference between the high dose and the placebo group is at least as good as the target value (TV) and the $Z_{MAV,}$ the test statistic to test the null hypothesis that the difference between the high dose and the placebo group is no better than the minimum acceptable value (MAV).<br>• Section 6.1.2 Adverse Events of Special Interest: included cardiac events potentially associated with QT prolongation, aligned with study RSV3001.<br>• Section 6.3.1 Vital Signs Definitions:<br>o Clarified that vital signs abnormalities will be identified based on subject's age at the date/time of assessment.<br>o Clarified that maximum temperature per day of assessment will be identified regardless of source of data collection (investigator [on-site] vs caregiver [home]) and will be used in all subsequent analyses.<br>• Section 6.4.1 Electrocardiogram: clarified that ECG abnormalities will be identified based on subject's age at the date/time of assessment.<br>• Section 7 Virology:<br>o Added the NGS-read cut-off frequencies.<br>o Updated long list of 20 F gene positions of interest to 24 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.<br>o Viral sequencing analysis methods clarified.<br>• Section 8 Impact of Pandemic: section added with overview of data handling to ensure COVID-19 impact transparency.<br>Additional minor clarifications and corrections were made throughout the document to align with clarifications and corrections noted above. |

# 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 |
| ClinRO | clinician reported outcomes |
| CPAP | Clinical Pharmacology Analysis Plan |
| CRF | case report form |
| CSR | Clinical Study Report |
| CV | coefficient of variation |
| DPS | Data Presentation Specifications |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| HR | Heart Rate |
| IA | interim analysis |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| ITT-i | Intent-To-Treat-infected |
| IQ | Interquartile |
| IQR | interquartile range |
| IWRS | interactive web-based response system |
| LLOQ | lower limit of quantification |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| ObsRO | observer reported outcomes |
| PD | pharmacodynamic(s) |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRESORS | Pediatric RSV Electronic Symptom and Outcomes Rating System |
| qRT-PCR | quantitative reverse transcription polymerase chain reaction |
| RAND | Randomized |
| RR | Respiratory Rate |
| RSV | respiratory syncytial virus |
| RT | Randomized or treated |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Sponsor Committee |
| SD | standard deviation |
| SE | standard error |
| SI | International System of Units |
| SOC | Standard of care |
| $SpO_2$ | peripheral capillary oxygen saturation |
| TEAE | treatment-emergent adverse event |
| TD | target detected |
| TND | target not detected |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for study RSV2002 including efficacy and safety of the

investigational compound JNJ-53718678. The SAP is to be interpreted in conjunction with the protocol.

This SAP covers the final analysis, as well as the interim analyses (IAs). Details on the Independent Data Monitoring Committee (IDMC) analyses will be provided in a separate IDMC SAP.

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

JNJ-53718678 is an investigational respiratory syncytial virus (RSV) specific fusion inhibitor belonging to the indole chemical class and under development for the treatment of RSV infection.

## 1.1. Trial Objectives

The primary objective is to establish antiviral activity of JNJ-53718678 as measured by RSV viral load in nasal swab samples by a quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay in children ≥28 days and ≤3 years of age with RSV disease.

The secondary objectives are to evaluate in children ≥28 days and ≤3 years of age with RSV disease:

- the dose-response relationship for antiviral activity of JNJ-53718678
- the impact of JNJ-53718678 on the clinical course of RSV infection
- the safety and tolerability of JNJ-53718678 after repeated oral doses
- the PK of JNJ-53718678 after repeated oral doses
- medical resource utilization
- the impact of baseline characteristics on antiviral activity and clinical course, including but not limited to:
  - time of symptom onset (≤3 days vs >3 days before start of treatment)
  - patient population (hospitalized subjects vs outpatients)
  - baseline viral load
  - disease severity at baseline
- the relationship between the PK and the PD (selected antiviral activity, clinical outcomes, and safety parameters) after repeated dosing of JNJ-53718678
- the emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678
- the acceptability and palatability of the JNJ-53718678 formulation

The exploratory objectives are to explore in children ≥28 days and ≤3 years of age with RSV disease:

- the impact of additional baseline characteristics on antiviral activity and clinical course, including but not limited to:
  - RSV viral subtype and genotype
  - baseline neutrophil count
- the occurrence of complications associated with RSV per investigator assessment after initiation of treatment
- the need for antibiotics related to complications associated with RSV per investigator assessment
- the relationship between antiviral activity and clinical outcomes
- the RSV viral load as measured by a qRT-PCR assay in nasopharyngeal and/or tracheal aspirate samples in a subgroup of hospitalized subjects (Cohort 1 only) in which these samples are obtained as part of their standard-of-care (SOC)
- the RSV infectious virus load as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay)

## 1.2. Trial Design

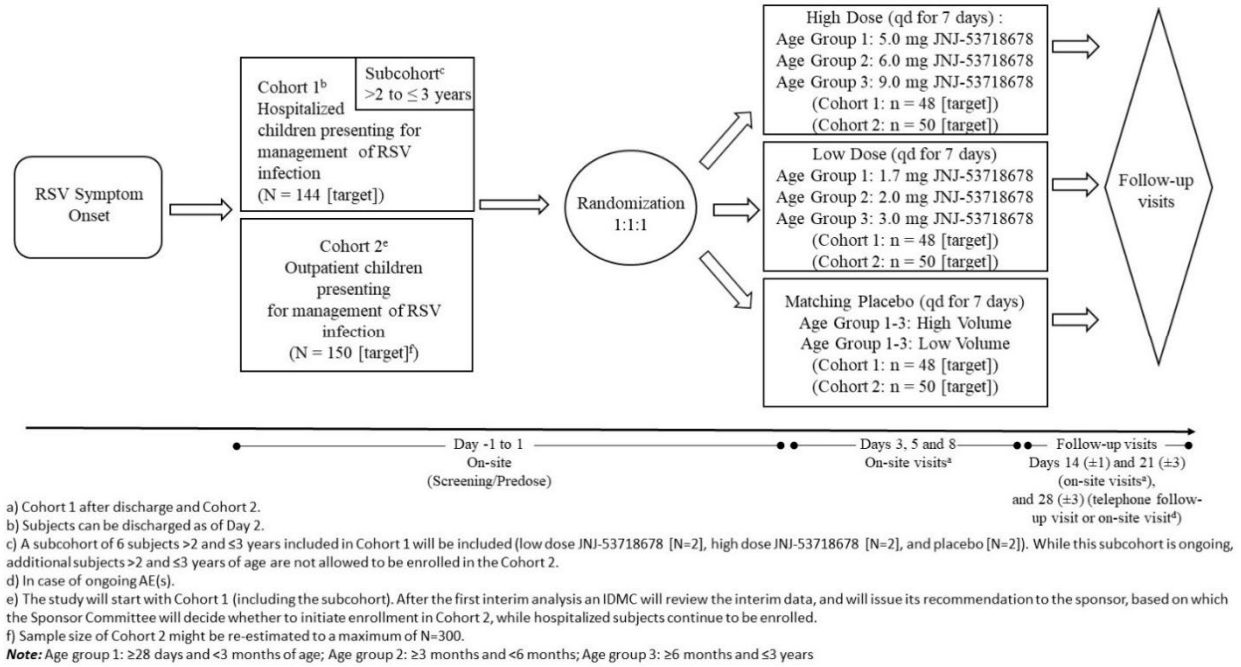
This is a Phase 2 multicenter, double-blind, placebo-controlled, randomized study to evaluate the antiviral activity, clinical outcomes, safety, tolerability, and PK/PD relationships of different oral dose levels of JNJ-53718678 in children ≥28 days and ≤3 years of age with RSV disease (hospitalized subjects [Cohort 1] or outpatients [Cohort 2]).

Up to 4 IAs are planned for this study. For the full trial design please refer to Section 3.1 of the protocol.

The total number of subjects is planned to be approximately 294 (approximately 144 in Cohort 1 and approximately 150 in Cohort 2; approximately 196 subjects receiving JNJ-53718678 and approximately 98 subjects receiving placebo). The sample size of Cohort 2 may be re-estimated to a maximum of 300 in Cohort 2 based upon results from the third IA.

Overall, for both cohorts, the study will include 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 will be approximately 29 days (Screening included). A diagram of the study design is provided in Figure 1.

**Figure 1: Schematic Overview of the Design of Study 53718678RSV2002**




a) Cohort 1 after discharge and Cohort 2.
b) Subjects can be discharged as of Day 2.
c) A subcohort of 6 subjects >2 and ≤3 years included in Cohort 1 will be included (low dose JNJ-53718678 [N=2], high dose JNJ-53718678 [N=2], and placebo [N=2]). While this subcohort is ongoing, additional subjects >2 and ≤3 years of age are not allowed to be enrolled in the Cohort 2.
d) In case of ongoing AE(s).
e) The study will start with Cohort 1 (including the subcohort). After the first interim analysis an IDMC will review the interim data, and will issue its recommendation to the sponsor, based on which the Sponsor Committee will decide whether to initiate enrollment in Cohort 2, while hospitalized subjects continue to be enrolled.
f) Sample size of Cohort 2 might be re-estimated to a maximum of N=300.
***Note:*** Age group 1: ≥28 days and <3 months of age; Age group 2: ≥3 months and <6 months; Age group 3: ≥6 months and ≤3 years

In Cohort 1, a subcohort of 6 subjects >2 and ≤3 years will be included, who will follow in general the same assessment schedule as for all subjects enrolled in Cohort 1, although with a specific PK sampling schedule, assigned at randomization. Of note, if the subcohort is fully enrolled, additional subjects >2 and ≤3 years of age can be enrolled in Cohort 1 and will follow all Cohort 1 procedures. Within each cohort, except for the subcohort, randomization will be stratified by time of symptom onset (≤3 days vs >3 days to ≤5 days before randomization) and by presence of risk factors for severe RSV disease (otherwise healthy vs presence of [a] risk factor[s] for severe RSV disease). Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45 % of all enrolled subjects in Cohorts 1 and 2 (i.e. maximum 55% of subjects can be enrolled in the >3 days stratum), To guarantee balance between strata for the IA, enrollment in the >3 days since symptoms onset stratum might be temporarily paused prior to an interim analysis and stopped prior to the final analysis. More details regarding randomization can be found in Section 1.5.

For dosing purposes, 3 age groups are defined depending on the subject's age at the time of consent:

- Age group 1: ≥28 days and <3 months of age (28 to 91 days of age, extremes included, for IWRS purposes)
- Age group 2: ≥3 months and <6 months of age (92 to 182 days of age, extremes included, for IWRS purposes)
- Age group 3: ≥6 months and ≤3 years of age (183 to 1,096 days, extremes included, for IWRS purposes)

Prior to Amendment #4 (dated 26 May 2020): study drug to be administered once daily (*quaque die* [QD]) for a planned treatment duration of 7 days. Doses are based on bodyweight and age group, but are identical for both cohorts:

- High Dose (Cohort 1: n = 48 [target]; Cohort 2: n = 50 [target]):
  - Age group 1: 5 mg JNJ-53718678/kg bodyweight
  - Age group 2: 6 mg JNJ-53718678/kg bodyweight
  - Age group 3: 9 mg JNJ-53718678/kg bodyweight
- Low Dose (Cohort 1: n = 48 [target]; Cohort 2: n = 50 [target]):
  - Age group 1: 1.7 mg JNJ-53718678/kg bodyweight
  - Age group 2: 2 mg JNJ-53718678/kg bodyweight
  - Age group 3: 3 mg JNJ-53718678/kg bodyweight
- Placebo (Cohort 1: n = 48 [target]; Cohort 2: n = 50 [target]): those randomized to a placebo regimen will subsequently be randomized 1:1 to receive either:
  - High volume placebo:
    - Age groups 1, 2, and 3: matching placebo (volume of placebo suspension to match the calculated volume of the JNJ-53718678 suspension for the high dose)
  - Low volume placebo:
    - Age groups 1, 2, and 3: matching placebo (volume of placebo suspension to match the calculated volume of the JNJ-53718678 suspension for the low dose)

Post-amendment #4 (dated 26 May 2020): Cohort 1 enrollment complete with all randomized and treated subjects receiving once daily dosing for a planned treatment duration of 7 days. Cohort 2 enrollment continuing with study drug to be administered twice daily (*bis in die* [BID]) for a planned treatment duration of 7 days. Total planned 14 doses are based on bodyweight and age group, but total daily dose remains identical for both cohorts regardless of dosing regimen:

- High Dose (Cohort 2: n = 50 [target]):
  - Age group 1: 2.5 mg JNJ-53718678/kg bodyweight
  - Age group 2: 3.0 mg JNJ-53718678/kg bodyweight
  - Age group 3: 4.5 mg JNJ-53718678/kg bodyweight
- Low Dose (Cohort 2: n = 50 [target]):
  - Age group 1: 0.85 mg JNJ-53718678/kg bodyweight
  - Age group 2: 1.0 mg JNJ-53718678/kg bodyweight
  - Age group 3: 1.5 mg JNJ-53718678/kg bodyweight

- Placebo (Cohort 2: n = 50 [target]): those randomized to a placebo regimen will subsequently be randomized 1:1 to receive either:
  - High volume placebo:
    - Age groups 1, 2, and 3: matching placebo (volume of placebo suspension to match the calculated volume of the JNJ-53718678 suspension for the high dose)
  - Low volume placebo:
    - Age groups 1, 2, and 3: matching placebo (volume of placebo suspension to match the calculated volume of the JNJ-53718678 suspension for the low dose)

For analysis purposes, treatment groups will be analyzed and presented regardless of dosing regimen (QD or BID).

## 1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV (i.e. a decrease in RSV viral load area under the curve (AUC) from immediately prior to first dose of study drug [baseline] until Day 5), as assessed by a positive dose-response relationship of JNJ-53718678 compared to placebo.

## 1.4. Sample Size Justification

The basis of the sample size calculation are the antiviral activity data of Study 53718678RSV1005. In that study, the mean difference in RSV viral load AUC from baseline until Day 5 of the placebo group versus active (adjusted for baseline viral load) was estimated as 105 $\log_{10}$ copies.hour/mL (corresponding to a 25% reduction) and the standard deviation (SD) on the RSV viral load AUC as 85 $\log_{10}$ copies.hour/mL (corresponding to a coefficient of variation [CV] of approximately 20%).

Assuming a more conservative reduction in RSV viral load AUC of 20% compared to placebo, considering a CV of 35% (slightly higher variability than observed in Study 53718678RSV1005), and a 1-sided alpha of 2.5%; the power to conclude a dose-response using the Multiple Comparison Procedure-Modeling (MCP-Mod) procedure under different assumptions for the dose-response relationship (linear, $E_{max}$ and exponential) is provided in Table 1. Based on Study 53718678RSV1005 results, no discrimination between the proposed doses is expected (i.e. $E_{max}$ dose-response shape was observed).

**Table 1: Power (%) to Conclude Dose-response Using MCP-Mod Under Different Assumptions for the Dose-response Relationship**

| Assumed CV | Assumed dose-response relationship | | |
|---|---|---|---|
| | **Linear** | **$E_{max}$** | **Exponential** |
| | **Cohort 1 + Cohort 2 (N=74 per treatment arm)** | | |
| 20% | 100.0 | 100.0 | 100.0 |
| 35% | 92.3 | 95.3 | 96.6 |
| | **Cohort 2 only (N=50 per treatment arm)** | | |
| 20% | 99.8 | 100.0 | 100.0 |
| 35% | 79.0 | 84.0 | 86.9 |
| | **Cohort 1 only (N=24 per treatment arm)** | | |
| 20% | 91.5 | 94.7 | 96.2 |
| 35% | 47.1 | 51.2 | 54.7 |

If data of both cohorts are combined (N=74 per treatment arm), the power to conclude dose-response is more than 90% for all 3 different assumptions for the dose-response relationship. If data from Cohort 1 cannot be combined with data from Cohort 2 (e.g. due to inconsistency [means and/or variability] in viral load data between cohorts per treatment group), the power to conclude a dose-response using the MCP-Mod procedure in Cohort 2 (N=50 per treatment arm) is at least 79%.

The sample size in Cohort 1 only ($n \geq 24$ per treatment arm) will provide sufficient power (approximately 90%) if the reduction in RSV viral load AUC is at least 20% with a CV which is not higher than observed in Study 53718678RSV1005 (i.e. 20%).

A sample size of 72 in Cohort 1 and 150 in Cohort 2 is sufficient to detect with reasonable power the antiviral effect; even if the data of Cohort 1 cannot be combined with the data of Cohort 2. Therefore, the primary analysis will be performed after approximately 150 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier). By that time, it is expected that at least 72 subjects from Cohort 1 will have completed the Day 14 assessments (or discontinued earlier).

For Cohort 1, assuming a median time to resolution of symptoms of 3 days in the placebo group, a 1-day reduction in the active group (i.e. ratio of 66%), and a scale parameter of 1/0.65, a sample size of 48 subjects per treatment arm will achieve 95% probability to reach an observed effect in the right direction based on estimates derived from an accelerated failure time model. This will allow an adequate evaluation of clinical course endpoints in the hospital population.

In conclusion, approximately 144 subjects in Cohort 1 (48 subjects per treatment arm) and approximately 150 in Cohort 2 (50 subjects per treatment arm) are planned to be recruited. The sample size of Cohort 2 may be re-estimated to a maximum of 300 in Cohort 2 based upon results from the third IA.

**Sample Size Re-estimation**

During IA#3 (when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments [or discontinued earlier]), a sample size re-estimation will be performed to allow an extension of Cohort 2 for the confirmation of the results on selected

clinical course endpoints. Based on all clinical course data from Cohort 2 available at the time of the cut-off for the third IA, one or more clinically relevant endpoint(s) will be selected for confirmation in the final analysis. Time to resolution (i.e. to none or mild symptoms) and reduction in severity of selected clinical signs/symptoms of RSV-related illness are currently expected to be the most relevant clinical endpoints for Phase 3 planning. However, data from this study, in combination with data from other RSV studies within and outside the company, and knowledge obtained through health authority interaction(s) will be considered in IA#3 for the endpoint selection and sample size recalculation for Cohort 2. After selection of (a) clinical endpoint(s), the number of subjects in Cohort 2 will be calculated that is required to minimize the conditional probability of inconclusive results (within the Go-NoGo approach) at the end of the study, assuming a required confidence of 80% (2-sided) to exclude the target value and/or the minimum acceptable value.

## 1.5. Randomization and Blinding

Central randomization will be 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. Within each cohort (including the subcohort of Cohort 1), eligible subjects will be randomized 1:1:1 to receive either a low or a high dose of JNJ-53718678, or placebo. Those randomized to a placebo regimen will be subsequently randomized in a 1:1 ratio to receive either low or high volume of placebo. This results in an overall randomization scheme of 2:2:1:1 (low dose JNJ-53718678, high dose JNJ-53718678, low volume placebo, high volume placebo). Randomization will be based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

In the subcohort of Cohort 1, next to randomization to treatment group, within each treatment arm (high dose, low dose, placebo), the 6 subjects will be randomized 1:1 to 1 of 2 different PK sampling groups. In Cohort 1, next to randomization to treatment group, the first 12 subjects of each age group (subcohort not included) will be randomized 1:1 to 1 of 2 different PK sampling groups. Once 12 subjects of a particular age group have been randomized to the 2 different PK sampling groups, the investigator can assign the subsequently enrolled subjects to either of the 2 PK sampling groups, but preferably alternating between 2 different PK sampling groups.

The randomization will be balanced by using randomly permuted blocks and will be stratified by time since symptom onset at randomization (≤3 days and >3 days) and by presence of risk factors for severe RSV disease (otherwise healthy vs presence of [a] risk factor[s] for severe RSV disease as defined above). Stratification will be applied to each cohort separately, with exception of the subcohort. Subjects with symptom onset ≤3 days before randomization must account for at least 45% of all enrolled subjects in Cohorts 1 and 2. To guarantee the required balance between strata for the interim analyses, enrollment in >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to an interim analysis and stopped prior to the final analysis.

# 2. GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.2 (or higher) and utilizing R version 3.6.3, where relevant.

## 2.1. Visit Windows and Phase Definitions

### 2.1.1. Analysis Phase Definitions

Analysis phases will be constructed as defined in Table 2.

**Table 2: Analysis Phases**

| Analysis Phase [number] | 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/time of first study drug administration in the trial | 23:59 of the last day of treatment + 3 days<br>or<br>23:59 of the cut-off date for the IA,<br><br>whichever comes first |
| **Follow-up [3]** | 1 minute after the End of Treatment Phase | 23:59 of the day of trial termination (date of last contact) or<br>23:59 of the cut-off date for the IA,<br><br>whichever comes first |

* For some sites, diagnostic ICF (Dx ICF) is required if RSV infection testing is not part of SOC or the SOC RSV diagnostic assay is not approved for use in the study. The earliest date between Dx ICF and main ICF will be used as a reference.

Assessments will be assigned to analysis phases based on their date/time, but seconds will be ignored overall. If the day part of the start date of the assessment is present but the time part is missing, the assessment will be treated as if it started at 00:00 on the day of the event (unless for Adverse Events see details in Section 6.1). If the day part of the end date of the assessment is present but the time part is missing, the assessment will be treated as if it happened at 23:59 on the day of the event. No formal imputation will be done, these rules will only be applied to allocate assessments to analysis phases.

### 2.1.2. 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:

- For 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.
- If none of the above, baseline, and subsequently change from baseline, will be considered missing.

- For Pediatric RSV Electronic Symptom and Outcome Rating System (PRESORS) clinician reported outcomes (ClinRO), clinical evaluation and parent/caregiver PRESORS observer reported outcomes (ObsRO), the baseline assessment will be defined as:
  - Last available assessment within the 8h prior to first drug intake.
  - If no assessment is available within 8h prior to first drug intake, but there is an assessment completed within 1h post first drug intake, then baseline assessment will be the assessment completed within 1h post first drug 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 none of the above, baseline, and subsequently change from baseline, will be considered missing.
- For electrocardiogram (ECG), triplicate 12-lead ECGs, approximately 1 minute apart and preferably all within 5 minutes should be performed. Baseline for continuous ECG parameters will be defined as:
  - Average of the last available complete ECG triplicate assessment prior to first dose of study drug.
  - In the absence of complete triplicate ECGs, the average of the last available ECG duplicate assessment will be considered.
  - In the absence of complete or partial triplicates, the last available single ECG can be used.
  - If none of the above, baseline, and subsequently change from baseline, will be considered missing.

A set of complete or partial triplicate ECG assessments is identified per date/time by a group identifier. Sequence number, within group identifier, can also be used to uniquely identify the relevant set of ECGs to be averaged. For continuous ECG parameters, all further analyses will be performed on the averaged ECG assessments only.

Once baseline is assigned, any assessment performed prior to the defined baseline, will be assigned to Screening. Screening visits will not be used in by-visit summary tables, only in listings. Any assessment performed after first dose of study drug on Day 1 and not considered baseline per the aforementioned definitions, will be assigned to Day 1, post-first dose of study drug (post-baseline).

### 2.1.3. Relative Day

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

The relative day will be defined as:

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

for visits on or after Day 1, and

$$reldy = visit\ date - reference\ date$$

for visits before Day 1.

There is no 'Day 0'.

### 2.1.4. Analysis Windows for Analysis Visits and Timepoints

Listed below are the visit windows and the target days for each visit defined in the protocol.

In general, the following rules will be applied in order 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 (the time of the assessment will be ignored, only the date component 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.

Exceptions to the general rule:

- *RSV RNA Viral Load*

  For the analyses of RSV RNA 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 the maximum RSV RNA viral load per day (regardless of sample collection setting [on-site vs homebased] and time of collection). The maximum RSV RNA viral load on a day will be used in all subsequent RSV RNA viral load analyses (e.g. time to undetectable) and for analysis visit windowing. Identified RSV RNA viral load, as assigned per analysis visit based on these rules, will be used for all subsequent by-visit RSV RNA viral load analyses. Please notice that baseline RSV RNA viral load follows the rules described in Section 2.1.2.

- *Electrocardiogram*

  In case there is more than one assessment per analysis visit window, the following rules will be used for continuous ECG parameters, to assign only one averaged ECG assessment per analysis timepoint. Within defined visit windows:

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

- In the absence of complete triplicate ECGs, the average of the last available ECG duplicate should be considered.
- In the absence of complete or partial triplicates, the last available single ECG assessment can be used.
- If none of the above, averaged ECG assessment at the given analysis timepoint will be considered missing.

With the implementation of Amendment #4 (dated 26 May 2020), ECG assessments are to be collected around 1h post-dose on Study Day 1 and Study Day 3. On these days, a time window of 45 min to 90 min will additionally be applied after assigning the target day:

- If ECG assessment within the time window (1h post-dose [-15 min to +30min]), same general approach to be applied (i.e. complete triplicate to be considered first, else duplicate ECG assessment, otherwise single ECG assessment if no other available).
- If ECG assessment is not within the time window (1h post-dose [-15 min to +30min]), the averaged post-dose ECG assessment closest to the target time of 1h post-dose will be considered and again applying the same general approach.

Visit windows for VL and ECG/labs are defined as in Table 3.

**Table 3: Visit Windows**

| Analysis Visit [scheduled Analysis Visit No.] | TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)] | |
|---|---|---|
| | VL | ECG/ Safety Laboratory |
| **Baseline**^ [0] | <=1 [1] | <=1 [1] |
| **Day 1** | NA | 1h post-dose* ≥45 min to ≤90 min [1] |
| **Day 2** [2] | >1 to 2 [2] | |
| **Day 3** [3] | 3 [3] | 1h post-dose* ≥45 min to ≤90 min [3] |
| **Day 4** [4] | 4 [4] | |
| **Day 5** [5] | 5 [5] | |
| **Day 6** [6] | 6 [6] | |
| **Day 7** [7] | 7 [7] | |
| **Day 8** [8] | 8 [8] | 8-9 [8] |
| **Day 9** [9] | 9 [9] | |
| **Day 10** [10] | 10 [10] | |
| **Day 11** [11] | 11 [11] | |

**Table 3: Visit Windows**

| Analysis Visit [scheduled Analysis Visit No.] | TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)] | |
|---|---|---|
| | VL | ECG/ Safety Laboratory |
| **Day 12** [12] | 12 [12] | |
| **Day 13** [13] | | |
| **Day 14** [14] | 13-15 [14] | |
| **Day 15** [15] | | |
| **Day 16** [16] | | |
| **Day 17** [17] | | |
| **Day 18** [18] | | |
| **Day 19** [19] | | |
| **Day 20** [20] | | |
| **Day 21** [21] | 18-24 [21] | 18-24 [21] |
| **Day 22** [22] | | |
| **Day 23** [23] | | |
| **Day 24** [241] | | |
| **Day 25** [25] | | |
| **Day 26** [26] | | |
| **Day 27** [27] | | |
| **Day 28** [28] | | 25 to +∞ [28] |

^ Baseline is defined as the last measurement before first study drug intake. Please also see Section 2.1.2

* With the implementation of Amendment #4 (dated 26 May 2020), ECG assessments are to be collected around 1h post-dose on Study Day 1 and Study Day 3. On these days, a time window of 45 min to 90 min will additionally be applied after assigning the target day.

Assessments (scheduled or unscheduled) that occur outside the visit windows (i.e. visits not being performed per protocol), may be assigned a visit window for consistency (based on the relative day). However, these assessments per assigned visits (outside the protocol schedule) will not be used in by-visit summary tables and figures but will only be shown in individual listings and figures. It should be noted that such assessments will still contribute to the identification of worst and emergent toxicity grades/abnormalities, as relevant.

PRESORS ClinRO, Clinical evaluation and PRESORS ObsRO are collected as per Table 4. The assessments are performed either BID or QD.

**Table 4: Planned Collection of PRESORS ClinRO, PRESORS ObsRO and Clinical Evaluation**

| Assessments | Cohort 1 | | Cohort 2 |
|---|---|---|---|
| | During Hospitalization | After Discharge | |
| **PRESORS ClinRO** | BID from Day 1 to Day 14 and QD from Day 15 to Day 21 | Once at clinic visits | Once at clinic visits |
| **Clinical Evaluation[£]/ SBP+DBP** | BID from Day 1 to Day 21 + Day 28* | Once at clinic visits + Day 28* | Once at clinic visits + Day 28* |
| **PRESORS ObsRO** | BID from Day 1 to Day 14 and QD from Day 15 to Day 21 | | |
| **Body Temp Caregiver** | NA | BID from Day 2 to Day 14 and QD from Day 15 to Day 21 | BID from Day 1 to Day 14 and QD from Day 15 to Day 21 |

[£] Clinical evaluation includes respiratory rate, heart rate, body temperature, and SpO2.
* Only in case of on-site visit.

Visit windows for these assessments are defined as in Table 5.

**Table 5: Visit Windows for PRESORS ClinRO, PRESORS ObsRO, Clinical Evaluation (including SBP/DBP) and Body Temperature**

| Analysis Time | Time Interval | Target Time |
|---|---|---|
| Baseline | | 0 |
| 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 |

**Table 5: Visit Windows for PRESORS ClinRO, PRESORS ObsRO, Clinical Evaluation (including SBP/DBP) and Body Temperature**

| Analysis Time | Time Interval | Target Time |
|---|---|---|
| 300h (Day 13.5) | 294h; 305h 59min | 300h |
| 312h (Day 14.0) | 306h; 317h 59min | 312h |
| Day 15 | Day [15]<br>(2 AM-1:59 AM) | 15 |
| Day 16 | Day [16]<br>(2 AM-1:59 AM) | 16 |
| Day 17 | Day [17]<br>(2 AM-1:59 AM) | 17 |
| Day 18 | Day [18]<br>(2 AM-1:59 AM) | 18 |
| Day 19 | Day [19]<br>(2 AM-1:59 AM) | 19 |
| Day 20 | Day [20]<br>(2 AM-1:59 AM) | 20 |
| Day 21 | Day [21]<br>(2 AM-1:59 AM) | 21 |
| Day 22 | Day [22]<br>(2 AM-1:59 AM) | 22 |
| Day 23 | Day [23]<br>(2 AM-1:59 AM) | 23 |
| Day 24 | Day [24]<br>(2 AM-1:59 AM) | 24 |
| Day 28 | Day [25, +∞]<br>(2 AM-1:59 AM) | 28 |

[$] Post-baseline (excluding assessments completed within 1h post-first dose of study drug on Day1 which are considered as baseline).

From Day 15 onwards, relative day (adjusted by timeframe as in the table) will be used to define analysis visits. In case there is more than one assessment per analysis visit, the one closest to the target will be used for the summary table per analysis visit. If more than one is equally close, then the last one will be considered in the analysis.

Note: in case there is an assessment on Day 14 not covered in the 312h window, it will not be used in by-visit summary tables and figures but will only be shown in individual listings and figures. Such assessments will contribute to time to event analyses, identification of abnormalities etc., as relevant.

For analyses for which we need at most one assessment per day (e.g. for summarizing combined in- and outpatient data captured by the clinician), we take the worst over 24 hours according to Table 6.

**Table 6: Worst per Day**

| Analysis time | Primary Selection ("worst hourly") | Secondary Selection* ("worst daily")<br>TIME INTERVAL (Day)<br>[TARGET TIMEPOINT (Day)] |
|---|---|---|
| Baseline | | |
| Day 2 | Worst [12h; 24h] | |
| Day 3 | Worst [36h; 48h] | 3<br>[3] |
| Day 4 | Worst [60h; 72h] | |
| Day 5 | Worst [84h; 96h] | 4-6<br>[5] |
| Day 6 | Worst [108h; 120h] | |
| Day 7 | Worst [132h; 144h] | |
| Day 8 | Worst [156h; 168h] | 8-9<br>[8] |

**Table 6: Worst per Day**

| Analysis time | Primary Selection ("worst hourly") | Secondary Selection* ("worst daily") TIME INTERVAL (Day) [TARGET TIMEPOINT (Day)] |
|---|---|---|
| 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] |
| Day 15 | Worst as per relative day (2 AM-1:59 AM) Relative day | |
| Day 16 | Worst as per relative day [16] (2 AM-1:59 AM) | |
| Day 17 | Worst as per relative day [17] (2 AM-1:59 AM) | |
| Day 18 | Worst as per relative day [18] (2 AM-1:59 AM) | |
| Day 19 | Worst as per relative day [19] (2 AM-1:59 AM) | |
| Day 20 | Worst as per relative day [20] (2 AM-1:59 AM) | |
| Day 21 | Worst as per relative day [21] (2 AM-1:59 AM) | 18-24 [21] |
| Day 28 | 25 to +∞ [28] | 25 to +∞ [28] |

*For ClinRO and Clinical Evaluation **only**: the secondary selection approach will be considered in the analysis **if** no record is assigned to Day 3, Day 5, Day 8, Day 14 and/or Day 21 according to the rules in the primary selection column in Table 6 (for subjects in Cohort 1 after hospital discharge, or for Cohort 2 subjects).

- If worst per day as per primary selection 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 result will be selected regardless of being the closest one to the target day.

Day 28 will always be assigned according to the window "25 to +∞". The primary and secondary selection for Day 28 will be identical as the same interval is used for both.

Additionally, each BID assessment is defined as a morning or evening assessment based on the timing of the assessment as defined in Table 7.

**Table 7: Time Slot in a Day for BID Days**

| 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

## 2.2. Pooling Algorithm for Analysis Centers

As it is anticipated that subjects will be recruited over a large number of centers, and the primary endpoint is a laboratory assessment (objective endpoint) evaluated by a central

assay, no heterogeneity of treatment effects across centers is expected. No pooling algorithm for analysis centers will be applied.

## 2.3. Analysis Sets

### 2.3.1. All Randomized Analysis Sets

#### 2.3.1.1. All Randomized Analysis (RAND) Set

All subjects randomized, regardless of being treated or not.

### 2.3.2. Efficacy Analysis Set(s)

The Intent-To-Treat-infected (ITT-i) set will be used to perform the evaluation of all efficacy variables including clinical course endpoints.

The primary endpoint (viral load) and key clinical course endpoints (time to resolution of key RSV symptoms, rate of RSV-related complications, change from baseline in key RSV symptoms) might also be analyzed on the Per Protocol (PP) set.

#### 2.3.2.1. ITT-i Set

All randomized subjects who received at least one dose of study drug and who have a centrally confirmed RSV RNA viral load of ≥1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) of the RSV RT-qPCR assay at baseline. Analyses on the ITT-i set will be performed as randomized.

#### 2.3.2.2. PP Set

All subjects in the ITT-i analysis set with the exclusion of any subjects deemed to have a major impact on the assessment of efficacy. The subjects to be excluded will be identified and documented prior to database lock based on the following criteria.

- Entered but did not satisfy criteria, violation of:
  - inclusion criteria 3, 4 or 5,
    AND/OR
  - exclusion criteria 5, 9, 10, 11, 12, 13 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 (including subjects who early discontinued study medication)

- Other:
  - Unplanned unblinding has taken place during the study
  - Insufficient post-baseline RSV RNA 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 identified and documented before the database lock.

- Missing PRESORS ObsRO:
  - at baseline
  - >1 missing for 4 consecutive assessments during BID schedule
  - >1 missing for 3 consecutive assessments during QD schedule

Note that in the PP set subjects will have been 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

The Safety analysis set includes all subjects who received at least 1 dose of study agent, and will be analyzed as treated, regardless of the randomized treatment group assigned. Where 'analyzed as treated' is defined as:

- Placebo: if only placebo doses received
- JNJ-53718678 Low/High dose: if at least one dose of active study drug received
  - Low dose: if majority of active doses received = low
  - High dose: if majority of active doses received = high

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

## 2.4. Definition of Subgroups

Table 8 defines subgroups of interest for investigation across several efficacy, safety, virology and other analysis endpoints (type of analysis = data domains). Refer to Section 5 for a detailed overview of efficacy endpoints (primary, secondary and exploratory).

The following data handling applies to subgroup presentation:

- With the exception of Region [Class 1], subgroups will only be presented if, based on total number of subjects across treatment groups:
  - Subgroups with two strata: N = 36 in both strata
  - Subgroups with more than two strata: N = 36 in at least one stratum

  Aforementioned data handling results in approximately 12 subjects minimum per treatment group with data in a stratum. This minimum number of subjects ensures sufficient data for meaningful subgroup analysis.
- Symptom onset:
  - Cohort 1: unless otherwise specified for a given endpoint, exploratory endpoints, as detailed in Section 5.4, will only be analyzed in the stratum: subjects with symptom onset ≤3 days before randomization. Subsequent subgroup analyses will be performed within this stratum only and also considering meaningful number of subjects as previously described.
  - In case of population enrichment decision (subjects with symptom onset ≤3 days before randomization), efficacy analyses will focus on those subjects with symptom onset ≤3 days before randomization stratum only. Subsequent subgroup analyses will be performed within this stratum only and also considering meaningful number of subjects as previously described.

- Table 8 provides a general overview of the subgroups to be investigated per type of analysis (data domain). For any given type of analysis, subgroup presentation will not be performed for all endpoints within the given domain but will be focused on the key outputs only. For example, 2 = viral load and 3 = clinical course endpoints below, all subgroups indicated in Table 8 will only be analyzed and presented for the primary endpoint and key clinical course endpoints (i.e. endpoints included in previous decision-making).
- Subgroup analysis and presentation may comprise tabulation of results and/or graphical presentation as best suits the purpose of the subgroup investigation. Specific details of- and format of subgroup analyses will be detailed in a separate document (data presentation specifications [DPS]) and is not included within the scope of this SAP.
- A listing of subject assignment to each of the subgroups defined in Table 8 will be provided.

**Table 8: Subgroups**

| **KEY:**<br>**1 = Demographics + Baseline Characteristics**<br>**2 = Viral Load 3 = Clinical Course Endpoints 4 = Hospitalized Subjects**<br>**5 = Exploratory Endpoints (Efficacy)**<br>**6 = Safety**<br>**7 = Virology** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Definition** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Cohort<br>[Class 1] | • Cohort 1: Hospitalized<br>• Cohort 2: Outpatient<br>Note: data collected from the subcohort of 6 subjects, >2 and ≤3 years, enrolled in Cohort 1 will be analyzed and presented as part of Cohort 1, no separate subcohort analyses will be provided. | X | X | X | X | X | X | X |
| Cohort<br>[Class 2] | Amendment #6 (dated 01 December 2020):<br>Lower respiratory tract infection (LRTI):<br>Signs/symptoms: Cough or wheezing should be accompanied by at least one additional LRTI sign/symptom in order to be eligible<br>• Cohort 1: Hospitalized (excluding subjects presenting with only cough or wheezing LRTI signs/symptoms)<br>• Cohort 2: Outpatient (excluding subjects presenting with only cough or wheezing LRTI signs/symptoms) | X | X | X | X | | | |
| Symptom Onset | • Subjects with symptom onset ≤3 days before randomization<br>• Subjects with symptom onset >3 days to ≤5 days before randomization<br>Note: derived strata as per electronic case report form (eCRF) information will be considered for the analyses. | X | X | X | X | X | X | |
| Age Group (months)<br>[Class 1] | • ≥28 days and <3 months<br>• ≥3 months and <6 months<br>• ≥6 months and ≤3 years<br>Note: based on collected age in days at Screening and converted to months. | X | X | X | X | X | X | |

| **KEY:**<br>**1 = Demographics + Baseline Characteristics**<br>**2 = Viral Load 3 = Clinical Course Endpoints 4 = Hospitalized Subjects**<br>**5 = Exploratory Endpoints (Efficacy)**<br>**6 = Safety**<br>**7 = Virology** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Definition** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Age Group [Class 2] | • <1 year<br>• ≥1 year | X | | | | | | |
| Presence of Risk Factors for Severe RSV Disease | • No<br>• Yes<br>Note: derived strata as per eCRF information will be considered for the analyses. | X | X | X | X | X | X | |
| Region [Class 1] | • Japan<br>• Non-Japan<br>Note: Japan region includes subjects from Country=Japan and Race=Asian | X | X | X | X | X | X | |
| Region [Class 2] | Based on country according to United Nations classification of geographic regions:<br>• Asia-Oceania (APAC)<br>• Europe and Middle East and Africa (EMEA)<br>• North America (NA)<br>• Latin America and the Caribbean (LATAM) | X | | | | X | | |
| Baseline RSV Viral Subtype | • RSV A<br>• RSV B<br>• RSV A+B | X | X | X | X | | | X |
| Presence of Other Respiratory Pathogens | • No<br>• Yes<br>Note: based on respiratory pathogens panel assays performed at baseline. | X | | X | X | X | | |
| Presence of Other Respiratory Viruses | • No<br>• Yes<br>Note: based on respiratory pathogens panel assays performed at baseline. | X | | X | X | X | | |
| Prior Use of Any Medications of Interest | • **No prior use**<br>• **Prior use of only one medication of interest**<br>Use of at least one of the below only:<br>○ Antitussives prior use only<br>○ Bronchodilators prior use only<br>○ Mucolytics prior use only<br>○ Inhaled corticosteroids prior use only<br>○ Systemic corticosteroids prior use only<br>• **Prior use of 2 or more medications of interest**<br>Note: medications of interest include: systemic and inhaled corticosteroids, antitussives, mucolytics and bronchodilators. | X | X | X | X | X | | |

| **KEY:**<br>**1 = Demographics + Baseline Characteristics**<br>**2 = Viral Load 3 = Clinical Course Endpoints 4 = Hospitalized Subjects**<br>**5 = Exploratory Endpoints (Efficacy)**<br>**6 = Safety**<br>**7 = Virology** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Definition** | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| Any Use of Medications of Interest (Prior and/or Concomitant) | • **No use**<br>• **Use of only one medication of interest**<br>Use of at least one of the below only:<br>○ Any use of Antibiotics only<br>○ Any use of Antitussives only<br>○ Any use of Bronchodilators only<br>○ Any use of Mucolytics only<br>○ Any use of Inhaled corticosteroids only<br>○ Any use of Systemic corticosteroids only<br>• **Any use of 2 or more medications of interest**<br>Note: medications of interest include: antibiotics, systemic and inhaled corticosteroids, antitussives, mucolytics, and bronchodilators. | X | X | X | X | X | | |

Medications of interest: programmatically identified based on World Health Organization-Drug Dictionary (WHO-DD) anatomic therapeutic (chemical) class (ATC) codes and product names. List of medications to be finalized in collaboration with medical review prior to use in analyses. Refer to Section 4.6 for further details.

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

Partial AE onset dates will be imputed as follows:

- 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.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the first dosing of the study medication
  - The time of the first dosing of the study medication if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

## 3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Up to four IAs are planned for this study (Figure 2):

i. The first IA will take place when at least 36 subjects from Cohort 1 have completed Day 14 assessments (or discontinued earlier) to evaluate safety and tolerability, PK, and antiviral effect.

ii. The second IA will take place preferably at the end of a hemispheric RSV season when approximately 70 to 80 subjects from Cohort 1 (regardless of the number of subjects in the subcohort having reached the target of 6 subjects) have completed Day 14 assessments (or discontinued earlier). Depending on enrollment status of Cohort 2, second IA will not be performed if later or too close to the estimated timing of the planned third IA. A futility and population enrichment analysis will be performed on antiviral activity (data from both cohorts combined), to terminate the study for futility, or to enrich the population and limit further enrollment to patients with ≤3 days since symptom onset. In addition, clinical course and safety-related endpoints, will be analyzed.

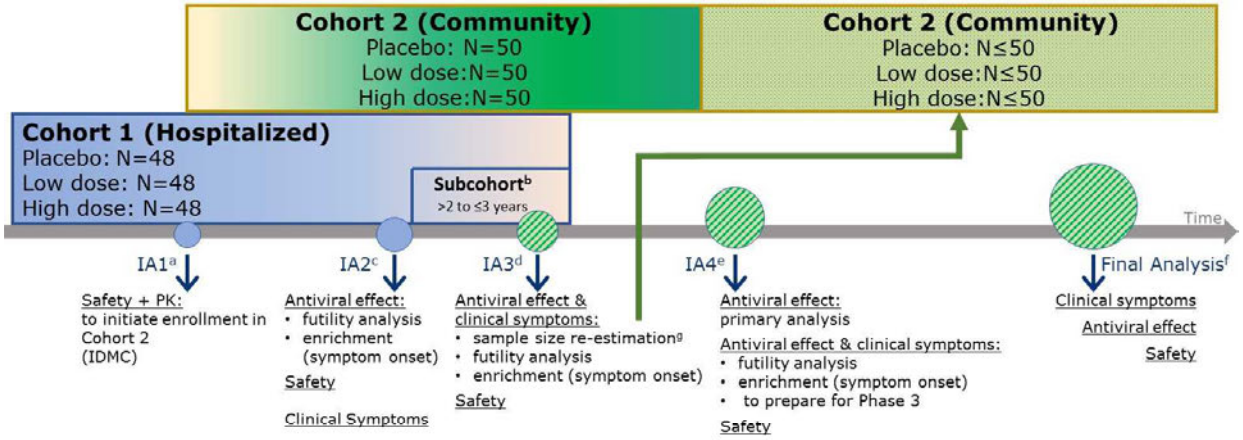
iii. The third IA will take place preferably at the end of a hemispheric RSV season, when approximately 70 to 80 subjects from Cohort 2 have completed Day 14 assessments (or discontinued earlier) and will include data from Cohort 1 and Cohort 2. This IA will include a futility and population enrichment analysis on antiviral activity (data from both cohorts combined) and clinical endpoints (data from Cohort 2 only), as well as a sample-size re-estimation for Cohort 2 based on clinical endpoints.

iv. The fourth IA will only take place if after third IA, decision is to increase number of subjects for Cohort 2. This IA will take place preferably at the end of a hemispheric

RSV season, after approximately 150 subjects in Cohort 2 completed Day 14 of assessments (or discontinued earlier) and will also include Cohort 1 subjects. The primary analysis on antiviral activity will be performed during this fourth IA and effects of JNJ-53718678 on clinical course endpoints, next to endpoints related to safety, PK and PK/PD, will be analyzed to support early Phase 3 plans.

The final analysis is planned when all subjects from Cohort 1 and Cohort 2 have completed the study (or discontinued earlier). If no extension of Cohort 2 is required, the final analysis may coincide with the primary analysis.

**Figure 2: Overview of Different Planned Analyses in Study 53718678RSV2002**




a) Planned when at least 36 subjects from Cohort 1 have completed the Day 14 assessments (or discontinued earlier). An IDMC will review the interim data, and will issue its recommendation to the sponsor, based on which the Sponsor Committee will decide whether to initiate enrollment in Cohort 2. The Sponsor Committee will take a decision considering the IDMC's recommendation.

b) A subcohort of 6 subjects >2 and ≤3 years included in Cohort 1 will be included (low dose JNJ-53718678 [N=2], high dose JNJ-53718678 [N=2], and placebo [N=2]). While recruitment in the subcohort of Cohort 1 is ongoing, subjects >2 and ≤3 years of age are not allowed to be enrolled in Cohort 2, even if enrollment in that cohort has been opened for the age groups ≤2. After 6 subjects of the subcohort are evaluable for PK analysis and have completed the Day 14 assessments (or discontinued earlier), safety and PK data will be reviewed by the IDMC, who will issue its recommendation to the sponsor, based on which the Sponsor Committee will decide whether to also initiate enrollment of subjects >2 and ≤3 years of age in Cohort 2 when enrollment in that cohort has been opened for the age groups ≤2. During this IDMC review, additional subjects >2 and ≤3 years of age can be enrolled in Cohort 1 and will follow all Cohort 1 procedures.

c) Planned when approximately 70-80 subjects from Cohort 1 (regardless of the number of subjects in the subcohort having reached the target of 6) have completed the Day 14 assessments (or discontinued earlier).

d) Planned when approximately 70-80 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier).

e) If the study is extended beyond the initially planned sample size in Cohort 2 for the primary analysis (N=150), the fourth interim analysis will be conducted after approximately 150 subjects in Cohort 2 have completed the Day 14 assessments (or discontinued earlier).

f) Planned when all subjects from Cohort 1 and Cohort 2 have completed the study (or discontinued earlier). If no extension of Cohort 2 is required, the final analysis will coincide with the primary analysis.

g) Based on clinical symptoms only.

An IDMC will be commissioned for this study and will review unblinded safety data on a regular basis throughout the conduct of this study to ensure subject safety. At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments, or to halt a dose arm due to safety concerns. Based on the recommendations of the IDMC following these IAs/reviews of PK, efficacy, and safety data, changes to the study may be implemented. The IDMC will also review safety and PK data from the 6 subjects in the subcohort of Cohort 1 and the data of the IAs and provide recommendations to the Sponsor Committee (SC). The SC will take a decision considering the IDMC's recommendation. Efficacy analyses presented to the IDMC will be limited to the primary endpoint (viral load) and key clinical course endpoints (time to resolution of key RSV symptoms [ObsRO], rate of RSV-related complications, change from baseline in key RSV symptoms [ObsRO]).

Further details are available in the IDMC charter, including subsequent distribution of unblinded results following analyses at interim milestones. The decision rules to be applied are defined in Section 5.6.

This SAP covers analyses planned for the final analysis, as well as for IAs. The IDMC will review the following analyses at each interim milestone:

- IA#1 will include analysis on safety, PK (out of scope of this SAP) and (descriptive summaries) on viral load
- IA#2 will include analysis on safety, PK (out of scope of this SAP), viral load and key clinical course endpoints
- IA#3 and IA#4 will include analysis on safety, viral load and key clinical course endpoints

| **Overview of information to be provided by IA** | **IA# 1** | **IA# 2** | **IA# 3** | **IA# 4** |
|---|---|---|---|---|
| **DISPOSITION AND BASELINE CHARACTERISTICS** | | | | |
| Subject Disposition and Study Completion/Withdrawal Information | ←------- in every IA ------ → | | | |
| Demographics and Baseline Characteristics | | | | |
| **SAFETY** | | | | |
| Medical history | ←------- in every IA ------ → | | | |
| Concomitant medication | | | | |
| Adverse events | | | | |
| Safety Laboratory (Hematology, Clinical Chemistry, Urinalysis) | | | | |
| ECG | | | | |
| Vital Signs (including body temperature, respiratory rate and $SpO_2$) | | | | |
| **PK** | | | | |
| PK parameters | ←------- in every IA ------ → | | | |
| **EFFICACY** | | | | |
| Viral Load | ←------- in every IA ------ → | | | |
| Clinical Course (key) variables | | | | |
| Time to resolution of key RSV symptoms (ObsRO) | | X | X | X |
| Incidence of RSV-related Complications | | X* | X | X |
| Change from baseline in RSV summary parameter: key RSV symptoms (ObsRO) | | | X | X |

* Only overview information and not considered for decision rules.

IA#3 and IA#4 will include at a minimum the analyses presented to the IDMC but might be extended to support decision-making for further development of JNJ-53718678 and to support interactions with health authorities.

## 4. SUBJECT INFORMATION

All subject information analyses described in the following sections will be done on the ITT-i Set and the Safety Set, unless specified otherwise for a specific display (in the data presentation specifications [DPS] document). Subject information will be summarized by

cohort and combined. Refer to Section 2.4 for further details regards subgroup analysis, per the analyses detailed below.

## 4.1. Demographics and Baseline Characteristics

Table 9 presents a list of the demographic variables that will be summarized descriptively by cohort, by treatment group and overall.

**Table 9: Demographic Variables**

| | Summary Type |
|---|---|
| **Continuous Variables:** | |
| Age (months) | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]). |
| Weight at baseline (kg) | |
| Length/Height at baseline (cm) | |
| Head Circumference at baseline (cm) | |
| **Categorical Variables** | |
| Sex (male, female, unknown, undifferentiated) | Frequency distribution with the number (n) and percentage (%) of subjects in each category. |
| Age Group (≥28 days and <3 months, ≥3 months and <6 months, ≥6 months and ≤3 years) | |
| Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported) | |
| Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) | |
| Country | |
| Region [Class 1] (Japan, non-Japan) | |
| Region [Class 2]:<br>• Asia-Oceania (APAC)<br>• Europe and Middle East and Africa (EMEA)<br>• North America (NA)<br>• Latin America and the Caribbean (LATAM) | |

[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.

Table 10 presents a list of the baseline characteristics that will be summarized descriptively by cohort, by treatment group and overall.

**Table 10: Baseline Characteristics**

| | Summary Type |
|---|---|
| **Continuous Variables:** | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]). |
| Duration of RSV symptoms prior to randomization (days) | |
| Duration of RSV symptoms prior to first treatment (days) | |
| Post-gestational Age (weeks) | |
| Baseline RSV RNA viral load ($log_{10}$ copies/ml)* | |
| Baseline RSV RNA viral load ($log_{10}$ copies/ml)* by RSV Subtype | |
| Baseline RSV RNA viral load ($log_{10}$ copies/ml)* by symptom onset | |
| Respiratory Rate (breaths/min) | |
| Heart Rate (beats/min) | |
| Oxygen Saturation (%) | |
| Number of siblings within the household | |
| **Categorical Variables** | Frequency distribution with the number (n) and percentage (%) of |
| Baseline RSV Subtype (RSV A, RSV B, RSV A+B) | |
| Symptom Onset (≤3 days, >3 days) at Randomization | |

**Table 10: Baseline Characteristics**

| | **Summary Type** |
|---|---|
| (i.e. stratification factor as entered in IWRS) | subjects in each category. |
| Presence of risk factors for severe RSV disease (no, yes) | |
| Each of the following risk factors for severe RSV disease (subcategories of the above):<br>- prematurity at birth<br>- bronchopulmonary dysplasia<br>- congenital heart disease<br>- Down syndrome<br>- neuromuscular impairment<br>- cystic fibrosis<br>- recurrent wheezing/asthma<br>- other congenital disease<br>- other | |
| Receiving Supplemental Oxygen prior to first intake of study medication (no, yes) | |
| Prenatal Smoking by the subject's mother (no, yes) | |
| Exposed to tobacco smoke in home environment (no, yes) | |
| History of wheezing associated with acute respiratory infection (no, yes) | |
| History of atopic dermatitis (eczema) (no, yes) | |
| History of allergy (no, yes) | |
| If yes, type of allergy (allergic dermatitis, allergic rhinitis, allergic bronchitis, food allergy) | |
| History of asthma (no, yes) | |
| Contact with HCP before presenting (no, yes) | |
| If yes, type of HCP (General Practitioner, Pediatrician, Other) | |
| Breastfeeding (no, yes) | |
| Routinely attending daycare (no, yes) | |
| Received palivizumab (no, yes) | |
| Received aerosolized ribavirin (no, yes) | |
| Received IV immunoglobulin (no, yes) | |
| Presence of other respiratory pathogens (No vs Yes) | |
| Presence of other respiratory viruses (No vs Yes) | |
| Presence of respiratory bacteria (No vs Yes) | |
| Prior use of antitussives<br>• No: No prior use<br>• Yes: Any prior use | |
| Prior use of bronchodilators<br>• No: No prior use within the 24h before first dose of study drug<br>• Yes: Any prior use within the 24h before first dose of study drug | |
| Prior use of mucolytics<br>• No: No prior use<br>• Yes: Any prior use | |
| Prior use of inhaled corticosteroids<br>• No: No prior use or use to a maximum of 2 consecutive days<br>• Yes: Any prior use for a minimum of 3 consecutive days | |
| Prior use of systemic corticosteroids<br>• No: No prior use or use to a maximum of 2 consecutive days<br>• Yes: Any prior use for a minimum of 3 consecutive days | |
| Prior use of any medication of interest<br>• No prior use | |

**Table 10: Baseline Characteristics**

| | Summary Type |
|---|---|
| • Prior use of only one medication of interest<br>• Prior use of 2 or more medications of interest | |

* Only nasal swab type samples to be considered.
Medications of interest: programmatically identified based on WHO-DD ATC codes and product names. List of medications to be finalized in collaboration with medical review prior to use in analyses. Refer to Section 4.6 for further details.

Duration of RSV symptoms prior to randomization will be calculated by considering:

- Symptom onset start date and time slot of the day (refer to Table 11: Time Slot in a Day)
- Randomization date and time slot of the day (refer to Table 12: Correction Factor for Time Slot in a Day)

**Table 11: 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 05:59 pm) |
| Evening | 18:00 (or 06:00 pm) – 23:59 (or 11:59 pm) |

*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 12: 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. A similar definition will be used for duration of RSV symptoms prior to first treatment.

A contingency table summarizing the mismatches between collected IWRS stratification factors and derived stratification factors (based on eCRF data) will be provided. In addition, those subjects with mismatches will be flagged and presented as part of the by-subject randomization listing.

## 4.2. Disposition Information

Summaries will be provided for the following disposition information by cohort, by treatment group and overall

- Subjects randomized:
  - Subjects randomized and not treated
  - Subjects randomized and treated
- Subjects in the Safety analysis set
- Subjects in the ITT-i analysis set
- Subjects assigned to the PP analysis set
- Subjects who completed treatment
- Subjects who prematurely discontinued study drug
  - Reasons for premature discontinuation of study drug
- Subjects who completed study
- Subjects who prematurely discontinued study participation
  - Reasons for premature discontinuation of study participation

Aforementioned summaries will be presented by planned treatment group (as randomized) with the exception of subjects assigned to safety- and PP analysis sets where the summaries will be presented by actual treatment received.

The following will be presented as part of by-subject data listings:

- Screen failure subjects and reasons for screen failure
- Subjects who discontinued study drug
- Subjects who discontinued study participation
- Subjects who were unblinded during the study period following randomization

## 4.3. Treatment Compliance

Compliance with study drug administration will be summarized descriptively by cohort, by treatment group and overall. The reasons for study drug not administered, vomiting after study drug administration and swallowing of full volume of suspension will be listed only. Compliance will be derived as:

> *treatment compliance (%) = 100 x number of doses administered/total number of doses planned per actual exposure*

Where total number of planned doses are as follows:

- Prior to Amendment #4 (dated 26 May 2020): study drug administered once daily:
  - For subjects who complete 7 days of planned treatment, a total number of 7 consecutive doses are to be administered as per protocol.
  - In case of premature discontinuation of study drug, total number of doses will be based on the number of days the subject was on treatment (e.g. 1 dose per

day is planned per protocol so if subject is treated for 3 days , total number of planned doses = 3 [1 day = approximately 24 hours = 1 dose planned]).

- Post-amendment #4 (dated 26 May 2020): study drug administered twice daily:
    - For subjects who complete 7 days of planned treatment, a total of 14 consecutive doses are to be administered as per protocol.
    - In case of premature discontinuation of study drug, total number of doses will be based on the number of days the subject was on treatment (e.g. 2 doses per day are planned per protocol so if subject is treated for 3 days starting the morning of Day 1, total number of planned doses = 6 taking into account the time slot of the day of first dose of study drug [1 day = approximately 24 hours = 2 doses planned]).

Derived study drug compliance (%) will be categorized as follows:

- <80 %
- ≥80 % to ≤100 %
- >100 %

## 4.4. Protocol Deviations

All major protocol deviations will be tabulated and listed, by cohort, by treatment group and overall. Those that may affect the assessment of efficacy will be flagged (see Section 2.3.2.2).

## 4.5. Medical History and Family History

Reported general medical history conditions will be presented as number (n) and percentage (%) of subjects according to the Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT). Separate summary tables will be provided for subjects with risk factors for severe RSV disease.

Risk factors for severe RSV disease, general medical history and family records will also be listed.

## 4.6. Prior and Concomitant Medications

Medications taken from the date when the ICF is signed through the end of study will be summarized by cohort, by treatment group and overall, by preferred term using the World Health Organization-Drug Dictionary as frequency tables for the prior and concomitant medications separately:

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 has 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 date/times, 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.

All prior and concomitant medication will be listed.

In addition, the proportion (number [n] and percentage [%]) of subjects in the ITTI-i/Safety analysis set with prior-, concomitant- and any use of medications of special interest will be presented. These include antibiotics, antitussives, bronchodilators, mucolytics, inhaled and systemic corticosteroids according to the following categories:

**Prior use only:**

**Table 13: Prior Use of Medications of Interest**

| PRIOR USE | NO | YES |
|---|---|---|
| Antitussives | No prior use | Any prior use |
| Bronchodilators | No prior use within the 24h before first dose of study drug | Any prior use within the 24h before first dose of study drug |
| Mucolytics | No prior use | Any prior use |
| Inhaled corticosteroids | No prior use or use to a maximum of 2 consecutive days | Prior use for a minimum of 3 consecutive days |
| Systemic corticosteroids | No prior use or use to a maximum of 2 consecutive days | Prior use for a minimum of 3 consecutive days |
| Any medications of interest | No prior use | • Prior use of only one medication of interest:<br>o Antitussives prior use only<br>o Bronchodilators prior use only<br>o Mucolytics prior use only<br>o Inhaled corticosteroids prior use only<br>o Systemic corticosteroids prior use only<br>• Prior use of 2 or more medications of interest |

**Concomitant use only:**

**Table 14: Concomitant Use of Medications of Interest**

| CONCOMITANT USE | NO | YES |
|---|---|---|
| Antibiotics | No concomitant use | Any concomitant use |

| CONCOMITANT USE | NO | YES |
|---|---|---|
| Antitussives | No concomitant use | Any concomitant use |
| Bronchodilators | No concomitant use | Any concomitant use |
| Mucolytics | No concomitant use | Any concomitant use |
| Inhaled corticosteroids | No concomitant use | Any concomitant use |
| Systemic corticosteroids | No concomitant use | Any concomitant use |
| Any medications of interest | No concomitant use | • Use of only one concomitant medication of interest:<br>○ Antibiotics use only<br>○ Antitussives use only<br>○ Bronchodilators use only<br>○ Mucolytics use only<br>○ Inhaled corticosteroids use only<br>○ Systemic corticosteroids use only<br>• Use of 2 or more concomitant medications of interest |

## Any use (prior and/or concomitant):

**Table 15: Any Use of Medications of Interest**

| ANY USE | NO | YES |
|---|---|---|
| Antibiotics | No prior and/or concomitant use | Any prior and/or concomitant use |
| Antitussive | No prior and/or concomitant use | Any prior and/or concomitant use |
| Bronchodilators | No prior and/or concomitant use | Any prior and/or concomitant use |
| Mucolytics | No prior and/or concomitant use | Any prior and/or concomitant use |
| Inhaled corticosteroids | No prior and/or concomitant use | Any prior and/or concomitant use |
| Systemic corticosteroids | No prior and/or concomitant use | Any prior and/or concomitant use |
| Any medications of interest | No prior and/or concomitant use | • Use of only one prior and/or concomitant medication of interest:<br>○ Antibiotics use only<br>○ Antitussives use only<br>○ Bronchodilators use only<br>○ Mucolytics use only<br>○ Inhaled corticosteroids use only<br>○ Systemic corticosteroids use only<br>• Use of 2 or more prior and/or concomitant medications of interest |

Prior and/or concomitant medications of interest: incorporate the defined use of medications of interest as detailed in Table 13 and Table 14 above.

## 4.7. Respiratory Pathogens

Positive/negative results for identified non-RSV pathogens at baseline, as based on respiratory pathogens assay, will be presented by the following categories:

- Presence of other respiratory pathogens
- Presence of other respiratory viruses
- Presence of respiratory bacteria

Within each category, number (n) and percentage (%) of subjects with positive/negative results per pathogen will be summarized by cohort, by treatment group and overall. In case multiple results are available from multiple assays per pathogen, the subject will be considered positive for the specific pathogen if one or more results from the multiple assays are positive. For example, for Bordetella pertussis: at least two results may be available, one from the Pathofinder Respifinder 2SMART assay and one from the Fast Track Diagnostics Bordetella assay. If either or both results are positive, the subject will be considered positive for the presence of Bordatella pertussis.

# 5. EFFICACY

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

**Primary Endpoint**

The primary efficacy endpoint is the RSV viral load AUC from immediately prior to first dose of study drug through Day 5 derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs.

**Secondary Endpoints**

- virologic parameters derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs including:
  - RSV viral load and change from baseline over time
  - RSV viral load AUC from immediately prior to first dose of study drug (baseline) through Day 3, Day 8, and Day 14
  - time to undetectable RSV viral load
  - proportion of subjects with undetectable RSV viral load at each timepoint throughout the study
- clinical course related endpoints:
  - in hospitalized subjects and outpatients:
    - following endpoints will be based on the Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS) assessed throughout the study by parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) and by the investigator (clinician PRESORS) during scheduled visits:
      - duration and severity of signs and symptoms of RSV disease
      - change from baseline in parent(s)/caregiver(s) PRESORS scores (worsening or improvement)

- ♦ change from baseline in clinician PRESORS scores (worsening or improvement)
- ♦ time to resolution (i.e. to none or mild) of RSV symptoms
- ♦ time to improvement based on general questions on overall health
- ♦ proportion of subjects with improvement or worsening of RSV disease based on general questions on overall health
- ♦ time to return to pre-RSV health as rated by the parent(s)/caregiver(s)

o respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation ($SpO_2$) over time as measured by the investigator during scheduled visits. ***Note:*** if the subject is enrolled in the substudy of Study 53718678RSV2002, the same parameters as assessed by the biosensor will be recorded from the standard-of-care monitoring/assessments as part of the substudy assessments.

o body temperature as measured by the parent(s)/caregiver(s) and recorded in the temperature log on the electronic device

o need for (re)hospitalization during treatment and follow-up

– in hospitalized subjects only:

o time to age-adjusted normal values for otherwise healthy and to pre-RSV infection status for subjects with (a) risk factor(s) for severe RSV disease, for heart rate, respiratory rate, and/or blood oxygen level (i.e. without requirement of supplemental oxygen compared with pre-RSV infection status)

o time to discharge (from initial admission and from initiation of treatment)

o time to clinical stability, with clinical stability evaluated by the investigator (from initial admission and from initiation of treatment)

o need for and duration of intensive care unit (ICU) stay; 'need for ICU stay' is defined as follows:

- ♦ being admitted on the ICU (and ICU level of care is required)
- ♦ being admitted on the hospital ward, with or without supplemental oxygen, but deemed to require ICU level of care (e.g. not transferred to ICU due to bed availability)
- ♦ requiring ICU level of care is defined by some specific conditions:
  - o acute or imminent respiratory failure
  - o treatment of complicated acid-base or electrolyte imbalances
  - o cardiogenic shock
  - o acute congestive heart failure
  - o hemodynamic instability
- ♦ having other conditions requiring specialized equipment and/or staff competencies only available in the ICU

o need for and duration of supplemental oxygen (regardless of method used); need for supplemental oxygen' is defined by:

- ♦ requiring invasive mechanical ventilation
- ♦ receiving any oxygen support requiring intubation or extracorporeal oxygenation
- ♦ receiving invasive mechanical ventilation
- ♦ receiving supplemental oxygen through a face mask or nasal cannula and not being able to sustain a blood oxygen saturation of ≥92% when breathing room air for 15 minutes or less, tested once

o need for and duration of non-invasive ventilator support (e.g. continuous positive airway pressure) and/or invasive ventilator support (e.g. endotracheal-mechanical ventilation)

o need for hydration and/or feeding by IV administration or nasogastric tube; need for defined by <50% of normal oral intake

o time to clinical stability, defined as the time from initiation of study treatment until the time at which the following criteria are met:

- ♦ return to age-adjusted normal values for otherwise healthy and pre-RSV infection status for subjects with (a) risk factor(s) for severe RSV disease, for all of the following signs/symptoms of RSV disease:
  - ▪ heart rate; AND
  - ▪ respiratory rate; AND
  - ▪ blood oxygen level

AND

- ♦ no more oxygen supplementation for otherwise healthy subjects and subjects with (a) risk factor(s) for severe RSV disease

AND

- ♦ no more IV/nasogastric tube feeding/hydration in otherwise healthy subjects or return to pre-RSV status of IV/nasogastric tube feeding/hydration in subjects with (a) risk factor(s) for severe RSV disease

o time from initiation of study treatment until $SpO_2$ ≥92% and $SpO_2$ ≥95% on room air among subjects who were not on supplemental oxygen prior to the onset of respiratory symptoms

- safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), vital signs, throughout the study
- PK parameters of JNJ-53718678, as determined by population PK (popPK) modeling
- medical resource utilization
- acceptability and palatability of the JNJ-53718678 formulation as assessed through a questionnaire completed by parent(s)/caregiver(s) in the electronic device
- sequence changes (post baseline) in the RSV F gene, and other regions of the RSV genome (at the discretion of the sponsor's virologist), as compared with the baseline sequence

**Exploratory Endpoints**

- The occurrence of complications with onset after treatment initiation that are associated with RSV per investigator assessment:
  - bacterial superinfections (e.g. pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment)
  - otitis media, bronchiolitis, viral pneumonia
  - exacerbations of underlying pulmonary disease (e.g. asthma, cystic fibrosis, bronchopulmonary dysplasia)
  - exacerbations of underlying cardiovascular conditions
- the use of antibiotics related to complications associated with RSV per investigator assessment
- the RSV RNA viral load as measured by a qRT-PCR assay in nasopharyngeal and/or tracheal aspirate samples in a subgroup of hospitalized subjects in which these samples are obtained as part of their SOC
- comparison of RSV RNA viral load as measured by a qRT-PCR assay in nasal swabs and other samples (e.g. nasopharyngeal and/or tracheal aspirate samples)
- virologic parameters derived from the RSV viral load as measured by quantitative viral culture

## 5.1. Analysis Specifications

Primary, secondary and exploratory efficacy analyses described in the following sections will be analyzed and presented using primarily the ITT-i analysis set, unless otherwise specified.

Analyses will be performed combining Cohort 1 (hospitalized subjects) and Cohort 2 (outpatients subjects) as well as in each cohort separately except for IA#1 where data from subjects in Cohort 1 only are available. In each IA, the cohort/s information to be considered for decision-making is specified in Section 5.6. For subgroup analysis, please refer to Section 2.4 for further details.

For all the stratified statistical analyses, the derived randomization stratification factors (symptom onset [≤3 days vs >3 days to ≤5 days before randomization] and presence of risk factors for severe RSV disease [Yes vs No]) will be used instead of the randomization stratification factors as collected in IWRS. Exception is sensitivity analysis of the primary efficacy endpoint based on IWRS randomization stratification factors.

In addition to the analyses outlined in the subsequent sections, efficacy parameters and a selection of derived efficacy variables will be presented in by-subject data listings.

### 5.1.1. Level of Significance

The primary objective is to establish antiviral activity of JNJ-53718678. The primary efficacy endpoint is the RSV RNA viral load AUC from immediately prior to first dose of study drug through Day 5 ($AUC_{Day\ 5}$) derived from the RSV RNA viral load as measured by a qRT-PCR assay in nasal swabs. A hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating dose-

response trends and estimating the dose-response relationships. The dose-response will be tested at each (interim) analysis at alpha=2.5% (1-sided).

The primary analysis will only adjust for multiplicity with respect to the candidate models included into the MCP-Mod test. Due to the exploratory nature of the study, no adjustment for multiplicity due to sub-populations and adaptations will be considered in the primary analysis. A secondary analysis approach will be performed to control for multiplicity in the clinical course endpoints and for adaptations (see Section 5.2.3.2).

### 5.1.2. Data Handling Rules

**RSV RNA 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 RSV RNA viral load will be imputed with the midpoint on the log scale between the limit of detection (LOD) and LLOQ of the RSV qRT-PCR assay 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 RSV RNA viral load, all the RSV RNA 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 RSV RNA 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 copies/mL scale value and then use the $\log_{10}$ of the sum of the imputed value and the 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 as 0 $\log_{10}$.

## 5.2. Primary Efficacy Endpoint(s)

### 5.2.1. Definition

RSV RNA viral load will be measured in mid-turbinate nasal swab specimens using an RSV A/B qRT-PCR assay.

The primary efficacy endpoint is the RSV RNA viral load area under the curve (AUC) from immediately prior to first dose of study drug (baseline) through Day 5 ($AUC_{Day\ 5}$) derived from the RSV RNA viral load as measured by a qRT-PCR assay in nasal swabs.

### 5.2.2. Estimand

The primary efficacy endpoint is the RSV RNA viral load $AUC_{Day\ 5}$ in subjects from both cohorts (hospitalized and outpatient). The presence of a dose-response will be established using the model-based trend test (MCP-Mod) among two doses of JNJ53718678 versus treatment with placebo, in combination with SOC.

The primary estimates of the $AUC_{Day\ 5}$ will be derived from a mixed model (see Section 5.2.3 for the detailed specification). No explicit imputations of missing data from nasal swabs post-baseline will be done in this model, as this mixed model would allow to make inferences implicitly imputing the missing data under the missing at random assumption.

### 5.2.3. Analysis Method

Mean $log_{10}$ RSV RNA viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach (MMRM). The analysis model includes fixed (discrete) effect parameters for treatment, randomization stratification factors (derived), analysis visit and treatment-by-analysis visit interaction, as well as continuous covariates for baseline $log_{10}$ viral load and baseline $log_{10}$ viral load-by-analysis visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors. In case this model will not converge, the Toeplitz covariance structure will be applied. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

For subgroup analyses, the model will also include the subgroup variable as a covariate and the subgroup-by-treatment, subgroup-by-analysis visit and subgroup-by-analysis visit-by-treatment interactions. For details about subgroups please see Section 2.4.

A generalized MCP-Mod (1) approach at 1-sided alpha-level of 2.5% will be applied based on the estimated AUC treatment group effect and variance covariance matrix. Candidate models are given by the EMax (0.40428), Exponential (0.36411) and Linear model, with the aim to test for existence of drug-related effects. Each of the dose-response shapes in the candidate set will be tested using the corresponding contrast t-test statistic, employing a critical value derived for the maximum of the t-test statistics (based on the associated multivariate t-distribution) to ensure appropriate multiplicity correction that preserves a 1-sided 0.025 Type I error rate. A dose-response trend is established when the maximum of the t-test statistics exceeds the critical value.

MCP-Mod uses dose levels 0, 3 and 9 mg/kg which correspond to Placebo, Low and High dose respectively according to the dose/kg for age-group 3 as described in Section 1.2.

#### 5.2.3.1. Sensitivity Analyses

Utilizing the same methodology as described for the primary efficacy endpoint, three sensitivity analyses will be performed as follows:

- MMRM + MCP-Mod: repeat analysis but using IWRS randomization stratification factors in the model as opposed to the derived factors based on the collected eCRF data.
- MMRM + MCP-Mod: repeat analysis but using the PP analysis set (if >10% ITT-i subjects excluded from PP analysis set due to major protocol deviations).
- MMRM + MCP-Mod: repeat analysis but excluding nasal swab samples where:
    - Ribonuclease P (RNAse P [housekeeping gene]): result = Target Not Detected AND
    - RSV A: result = Target Not Detected AND
    - RSV B: result = Target Not Detected

#### 5.2.3.2. Methods to Control the Type I Error for Multiplicity and Adaptations

Due to the adaptive design, and multiple populations (i.e. full ITT-i analysis set and sub-population based on ITT-i subjects with symptom onset [≤3 days relative to randomization]), the Type I error will be controlled using the inverse-normal p-value-combination test as a secondary analysis approach. The total study alpha will be used at the timepoint for the primary analyses which are:

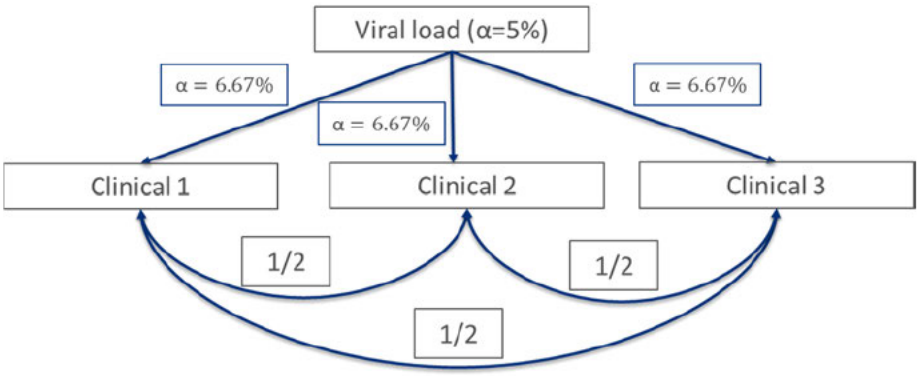
- Interim analysis 4 for antiviral effects (α=5%, i.e. 2.5% 1-sided)
- Final analysis for clinical course endpoints (α=20%, i.e. 10% 1-sided)

In a sequential testing framework, this corresponds to the following cumulative α-spending on primary and secondary endpoints:

| | IA#1 | IA#2 | IA# 3 | IA#4 | Final Analysis |
|---|---|---|---|---|---|
| Viral load | 0% | 0% | 0% | 5% | 5% |
| Clinical course | 0% | 0% | 0% | 0% | 20% |

This testing procedure will be applied on the ITT-i set

The primary endpoint on viral load ($AUC_{Day\ 5}$) will be tested at alpha of 5% (i.e. 2.5% 1-sided). To account for multiplicity in the statistical evaluation of the key clinical course secondary endpoints, a Bonferroni-Holm procedure will be applied to control for the overall Type I error rate. Clinical course endpoints are tested using an MCP-Mod test at 1-sided alpha level of 10%. Testing of the key clinical course endpoints (time to resolution of key RSV symptoms [ObsRO], incidence of RSV-related complications and change from baseline in key RSV symptoms [ObsRO]) will therefore be started at the 20/3 (6.667)% level. Levels used for testing will be adjusted, in case at least one of the key clinical course endpoints succeeds. The testing strategy is graphically summarized as:




The family wise error rate is strictly controlled at a level below 20% using the considered Bonferroni-Holm procedure.

The study design allows for enrichment at interim analyses 2, 3 and 4. The sample size re-estimation for clinical course endpoints will be conducted at interim analysis 3 only. To control for the multiple potential adaptations (enrichment and sample size re-estimation), the following procedures will be applied. All computations are to be conducted using stage-wise **1-sided** p-values. The final test decision is based on 2-sided p-values. Given the final 1-sided p-value, the 2-sided p-value results as:

- $p_{2-sided} = 2 \times \min\{p_{reported}, 1 - p_{reported}\}$

Let the cumulative sample sizes for Cohort i up to analysis j be defined as $n_{ij}$:

| | **IA#1** | **IA#2** | **IA#3** | **IA#4** | **Final Analysis** |
|---|---|---|---|---|---|
| Cohort 1 (n=144) | $n_{11}$ (~36) | $n_{12}$ (~75) | $n_{13}$ (~144) | $n_{14}$ (~144) | $n_{15}$ (~144) |
| Cohort 2 (n=150) | | $n_{22}$ (~36) | $n_{23}$ (~75) | $n_{24}$ (~150) | $n_{25}$ (~300) |

**RSV RNA Viral Load:**

The total sample size planned for the primary analysis on viral load is given as: $n_{Primary}$=294. This constitutes the sample size of both Cohorts 1 and 2.

Stagewise weights and 1-sided p-values are defined as:

| | **IA#2** | **IA#3** | **IA#4** |
|---|---|---|---|
| *No enrichment:* | | | |
| Weight | 1 | | |
| p-value | $p_{14}^F$ | | |
| Final p-value (global) | $p_{14}^F$ | | |
| Final p-value (sub) | $p_{14}^S$ | | |
| | | | |
| *Enrich at IA#2:* | | | |
| Weight ($w_{ij}$) | $(n_{12}+n_{22})/n_{Primary}$ | $(n_{Primary} - n_{12} - n_{22})/n_{Primary}$ | |
| p-value | $p_{12}^F$ | $p_{34}^S$ | |
| Final p-value (global) | $1 - \Phi\left(\sqrt{w_{12}}\Phi^{-1}(1 - p_{12}^F) + \sqrt{w_{34}}\Phi^{-1}(1 - p_{34}^S)\right)$ | | |

| | IA#2 | IA#3 | IA#4 |
|---|---|---|---|
| Final p-value (sub) | $1-\Phi\left(\sqrt{w_{12}}\Phi^{-1}(1-p_{12}^{S})+\sqrt{w_{34}}\Phi^{-1}(1-p_{34}^{S})\right)$ | | |
| | | | |
| *Enrich at IA#3:* | | | |
| Weight ($w_{ij}$) | $(n_{13}+n_{23})/n_{Primary}$ | | $(n_{Primary}-n_{13}-n_{23})/n_{Primary}$ |
| p-value | $p_{13}^{F}$ | | $p_{44}^{S}$ |
| Final p-value (global) | $1-\Phi\left(\sqrt{w_{13}}\Phi^{-1}(1-p_{13}^{F})+\sqrt{w_{44}}\Phi^{-1}(1-p_{44}^{S})\right)$ | | |
| Final p-value (sub) | $1-\Phi\left(\sqrt{w_{13}}\Phi^{-1}(1-p_{13}^{S})+\sqrt{w_{44}}\Phi^{-1}(1-p_{44}^{S})\right)$ | | |

- $p_{ij}^{F}$ defines the p-value for the MCP-Mod test for data collected from in stages i to j in the full population
- $p_{ij}^{S}$ defines the p-value for the MCP-Mod test for data collected from in stages i to j in the sub population

A p-value combination for the test of the sub-population is required, as the enrichment decision implies a sample size re-calculation for the sub-population.

**Clinical Course Endpoints:**

Sample size for clinical course endpoints is only based on Cohort 2. Let $n_{Primary} = 225$ be defined as midway between planned (N= 150) and maximum sample size (N=300).

| | IA#2 | IA#3 | IA#4 | Final Analysis |
|---|---|---|---|---|
| *No enrichment:* | | | | |
| Weight ($w_{ij}$) | $(n_{23})/n_{Primary}$ | | $(n_{Primary}-n_{23})/n_{Primary}$ | |
| p-value | $p_{23}^{F}$ | | $p_{45}^{F}$ | |
| Final p-value (global) | $1-\Phi\left(\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^{F})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{F})\right)$ | | | |
| Final p-value (sub) | $1-\Phi\left(\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^{S})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{S})\right)$ | | | |
| *Enrich at IA#2:* | | | | |
| Weight ($w_{ij}$) | $n_{22}/n_{Primary}$ | $(1-w_{22})*(n_{23}-n_{22})/(n_{Primary}-22)$ | $(1-w_{22})*[(n_{Primary}-n_{23})/(n_{Primary}-n_{22})]$ | |
| p-value | $p_{22}^{F}$ | $p_{33}^{S}$ | $p_{45}^{S}$ | |
| Final p-value (global) | $1-\Phi\left(\sqrt{w_{22}}\Phi^{-1}(1-p_{22}^{F})+\sqrt{w_{33}}\Phi^{-1}(1-p_{33}^{S})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{S})\right)$ | | | |
| Final p-value (sub) | $1-\Phi\left(\sqrt{w_{22}}\Phi^{-1}(1-p_{22}^{S})+\sqrt{w_{33}}\Phi^{-1}(1-p_{33}^{S})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{S})\right)$ | | | |
| *Enrich at IA#3:* | | | | |
| Weight ($w_{ij}$) | $n_{23}/n_{Primary}$ | | $(n_{Primary}-n_{23})/n_{Primary}$ | |
| p-value | $p_{23}^{F}$ | | $p_{45}^{S}$ | |
| Final p-value (global) | $\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^{F})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{S})$ | | | |
| Final p-value (sub) | $\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^{S})+\sqrt{w_{45}}\Phi^{-1}(1-p_{45}^{S})$ | | | |

| | IA#2 | IA#3 | IA#4 | Final Analysis |
|---|---|---|---|---|
| | | | | |
| *Enrich at IA#4:* | | | | |
| Weight ($w_{ij}$) [$] | $n_{23}/n_{Primary}$ | | $(1-w_{23})*(n_{24}-n_{23})/(n_{25;Replan}-n_{23})$ | $(1-w_{13})*(n_{25;Replan}-n_{24})/(n_{25;Replan}-n_{23})$ |
| p-value | $p_{23}^F$ | | $p_{44}^F$ | $p_{55}^S$ |
| Final p-value (global) | $1-\Phi\left(\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^F)+\sqrt{w_{44}}\Phi^{-1}(1-p_{44}^F)+\sqrt{w_{55}}\Phi^{-1}(1-p_{55}^S)\right)$ | | | |
| Final p-value (sub) | $1-\Phi\left(\sqrt{w_{23}}\Phi^{-1}(1-p_{23}^S)+\sqrt{w_{44}}\Phi^{-1}(1-p_{44}^S)+\sqrt{w_{55}}\Phi^{-1}(1-p_{55}^S)\right)$ | | | |

[$] The denominator changes as we have the new sample size. The planned sample size is covered in $w_{23}$ and $(1-w_{23})$. If study continues, the two new portions are identified as total $n_{25}$ and (replan-$n_{23}$) subjects.

In case of no sample size increase, the IA#4 will coincide with the final analysis. In this situation, no enrichment at IA#4 is possible, such that either "no enrichment", "enrich at IA#2" or "enrich at IA#3" will apply with p-values defined therein.

## 5.3. Secondary Endpoints

### 5.3.1. Definitions

#### 5.3.1.1. RSV RNA Viral Load (qRT-PCR)

The RSV RNA viral load AUC will be analyzed using one of two methods:

- Day 3 ($AUC_{Day\ 3}$) and Day 8 ($AUC_{Day\ 8}$): utilizing the same methodology as described for the primary efficacy endpoint (refer to Section 5.2.3 for details).
- Day 14 ($AUC_{Day\ 14/0\text{-}312h}$): trapezoidal method as defined below.

Formulae to be used for derived viral load parameters, are provided in Table16.

**Table 16: Viral Load Parameters**

| Measurement | Formula |
|---|---|
| $Log_{10}$ RSV RNA viral load actual values | $Log_{10}$ of the actual values as measured with qRT-PCR in nasal swab samples collected at the clinic visits and at home |
| $Log_{10}$ RSV RNA viral load change from baseline | *change = ($log_{10}$ RSV viral load actual value – $log_{10}$ RSV viral load baseline value)* |
| RSV RNA viral load $AUC_{0\text{-}312h}$ [trapezoidal method] | RSV RNA viral load $AUC_{0\text{-}312h}$ from 0 hours through 312h hours using the trapezoidal method (see below). |
| Time (hours) to virus undetectable [time to event] | Time to virus undetectable will be evaluated using two approaches:<br>1. Time to **undetectable** RSV RNA viral load: defined as the time in hours from first dose of study drug to first post-baseline timepoint |

**Table 16: Viral Load Parameters**

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>at which the virus is undetectable AND after which no more detectable virus assessments (=event).
<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>
<tr><td>Death (without previous undetectable)</td><td>date/time of death</td></tr>
</table>
2. Time to <u>confirmed undetectable</u> RSV RNA viral load: defined as the time in hours from first dose of study drug to first post-baseline timepoint at which the virus is <u>confirmed undetectable</u> (=event). A <u>confirmed undetectable</u> sample is defined as the first of at least two consecutive undetectable samples. 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>
<tr><td>Death (without previous confirmed undetectable)</td><td>date/time of death</td></tr>
</table>
time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><td>RSV RNA viral load status at each timepoint [categorical]</td><td>Each RSV viral load value will be assigned to one of the 3 categories below:<ul><li>Undetectable (<LLOQ TND)</li><li>Detectable (<LLOQ TD)</li><li>Quantifiable (>= LLOQ)</li></ul>Note : in case of co-infection with both RSV A and B, the worst category across subtypes will be used for analysis. Higher RSV viral load denotes worse degree of infection, thus ordering from ‘worst to better’ follows: Quantifiable – Detectable – Undetectable.</td></tr>
<tr><td>RSV RNA viral load status at each timepoint [binary]</td><td>Each RSV RNA viral load value will be assigned to one of the 2 categories:<ul><li>Detectable or quantifiable = Yes (1)</li><li>Undetectable = No (0)</li></ul>Note : in case of co-infection with both RSV A and B, the worst category across subtypes will be used for analysis. Higher RSV RNA</td></tr>
</table>

**Table 16: Viral Load Parameters**

| Measurement | Formula |
|---|---|
| | viral load denotes worse degree of infection, thus ordering from 'worst to better' follows: Quantifiable OR Detectable – Undetectable. |

**Trapezoidal Method:**

The trapezoidal method will be used to calculate RSV RNA viral load AUC between 0 and 312 hours (= Day 14), based on all date/times of viral load 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 timepoints 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 (= 312 hours).

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

1. The value at timepoint 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 post-dose observation.
3. The value at xx hours, if not exactly at xxh (or missing) and if not the last available observation, will be calculated based on linear 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 the last available observation should only be performed if the time between the last available observation and the value at xxh is at most 24 hours.
5. Missing values between 0h and xxh will be imputed by linear 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.

#### 5.3.1.2. Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS)

PRESORS Version 7.1, ObsRO scoring system, as used during this study is available in Attachment 2: PRESORS ObsRO Scoring System. PRESORS Version 7, ClinRO scoring system, as used during this study is available in Attachment 3: PRESORS CLINRO Scoring System.

#### 5.3.1.2.1. PRESORS Modified Definitions

Based on the PRESORS validation results of 64041575RSV0001 study and the IA of this study with data cut-off 02 January 2020 (Cohort 1= 115 subjects; cohort 2 = 40 subjects), modified scores will be defined implementing the following changes for concept scores and definition of resolution:

| PRESORS | CONCEPT/ Answer level | ORIGINAL | | MODIFIED | |
|---|---|---|---|---|---|
| | | Score | Definition | Score | Definition |
| **Caregiver (ObsRO)** | **Dehydration** 'Dry Skin or Lips' | 2 | Not Resolved | 1 | Resolved |
| | **Retractions** 'Belly Sucked In While Breathing' | 1 | Resolved | 2 | Not Resolved |
| | **Cyanosis** | Any | Any | Not Considered | |
| | **Apnea** | Any | Any | Not Considered | |
| **Clinician (ClinRO)** | **Retractions** 'Subcostal Retractions' | 1 | Resolved | 2 | Not Resolved |
| | **Cyanosis** | Any | Any | Not Considered | |
| | **Apnea** | Any | Any | Not Considered | |

PRESORS data will primarily be analyzed for IA#3 and onwards:

- Considering modified concepts scores and modified definition of resolution.
- The modified summary parameters for scores and time to resolution (Overall Symptoms, Key RSV Symptoms, Respiratory Symptoms and General Illness Behavior) will be derived excluding Cyanosis and Apnea and using modified concepts scores and modified definition of resolution (Dehydration and Retractions for ObsRO and Retractions for ClinRO).

Any decision rule that requires PRESORS data will be based on results with modified definitions.

The analyses based on original concepts scores, summary parameters and original definition of resolution will be provided as needed.

**PRESORS ObsRO:**

Based on collected data, the following are defined for analysis (refer to Table 17: Parameters based on PRESORS ObsRO):

**Table 17: Parameters based on PRESORS ObsRO**

| Measurement | Formula |
|---|---|
| ObsRO concept scores + change from baseline | Score per concept according to the score system provided in Attachment 2.<br><br>Each concept score ranges from 0 to 3. The higher the score, the worse the symptom/concept. |

**Table 17: Parameters based on PRESORS ObsRO**

| Measurement | Formula |
|---|---|
| ObsRO summary parameter scores + change from baseline | Average of the different concepts, ranging from 0 to 3.<br><br>Four summary parameters, for which a summary score will be derived: key RSV symptoms, respiratory symptoms, general illness behavior and overall RSV symptoms and will be calculated as defined in Attachment 2. |
| Daily summary scores | For each ObsRO summary parameter (x4), a daily summary score will be derived utilizing two approaches to identify the worst concepts score:<br><br>• **Average of the worst (PRIMARY APPROACH)**: daily summary score will be the average of the worst (highest) score reached per individual concept per day. Table Worst per Day (see Table 6) timepoints will be applied, resulting in a 'worst hourly' and 'worst daily' score. Note that unless otherwise stated, the daily summary score 'worst hourly' is the score considered in the analyses.<br><br>• **Worst of the average (SECONDARY APPROACH)**: daily summary score will be the worst (highest) summary score derived as the average of the relevant individual concepts scores per timepoint. Similarly, 'worst hourly' and 'worst daily' can be derived. As exploratory analysis, this secondary approach will be evaluated versus the primary approach 'average of the worst'.<br><br>The following illustrates the above two approaches for the summary parameter, key RSV symptoms:<br><br>breathing problems / retractions / tachypnea / breathing sounds / cough / tachycardia<br>morning: 3 / 2 / 0 / 2 / 3 / 0<br>evening: 2 / 2 / 1 / 1 / 1 / 0<br>worst in the day: 3 / 2 / 1 / 2 / 3 / 0<br><br>Key RSV Symptoms<br>average morning= 1.66666667<br>average evening = 1.16666667<br>worst of the average= 1.66666667<br>average of the worst = 1.83333333 |
| Time (hours) to resolution of RSV symptoms *[individual concepts]*<br><br>[time to event] | For ObsRO symptoms (concepts): sleep disturbance, crying, illness behavior, breathing problems, retractions, tachypnea, breathing sounds, cough, nasal secretions, tachycardia, feeding, dehydration:<br><br>Time (in hours) from first dose of study drug until first date/time of resolution of the RSV symptom (concept from ObsRO). *Where resolution is defined as a score of 0 (none) or 1 (mild) for approximately 24h*<br><br>Cyanosis and apnea will not be considered when modified definitions applied. |

**Table 17: Parameters based on PRESORS ObsRO**

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>The approximate 24h symptoms resolution is defined with the following considerations:<br>• 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 14. These 3 consecutive recordings should have been done over 4 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed.<br>• 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 14. These 2 consecutive recordings should have been done over 3 scheduled consecutive analysis timepoints, 1 missing timepoint is allowed<br>In case RSV symptoms (concepts) are not resolved, data will be censored as follows:
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last ObsRO assessment indicates resolution of RSV symptoms but insufficient recordings to meet the time to resolution requirement (24h)</td><td>Censored at first record of resolution from the last series of recordings of resolution of RSV symptoms (concepts)</td></tr>
<tr><td rowspan="3">Last ObsRO assessment does not indicate resolution of RSV symptoms</td><td>After the last observation, censored at 08:00 on the same day if the last observation was a morning diary entry (from 00:00 until 01:59)</td></tr>
<tr><td>After the last observation, censored 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>Censored at 8:00 the next day if the last entry was an evening diary entry(from 14:00 until 23:59)</td></tr>
<tr><td>Death (without previous resolution)</td><td>Censored at date/time of death</td></tr>
<tr><td>Missing information to determine resolution of symptoms (concepts) because of (re-)hospitalization (without previous resolution)</td><td>Censored at date/time of (re-)hospitalization</td></tr>
</table>
time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><td>Time (hours) to resolution of RSV [summary parameters]<br><br>[time to event]</td><td>For the 4 summary parameters:<br>• Key RSV symptoms<br>• Respiratory symptoms<br>• General illness behavior<br>• Overall RSV symptoms<br>Time (hours) from first dose of study drug until the date/time of first observed resolution of all individual RSV concepts (symptoms)</td></tr>
</table>

**Table 17: Parameters based on PRESORS ObsRO**

| Measurement | Formula |
|---|---|
| | comprising the relevant summary parameter (refer to Attachment 2 for concepts comprising each RSV summary parameter).<br><br>In case not all RSV concepts, comprising a summary parameter, are resolved, data will be censored. Similar rules as for time to resolution of each ObsRO individual symptom (concept) will be applied.<br><br>*time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Status of RSV symptoms at each timepoint [categorical] | Each assessment of 'Keeping in mind all the symptoms you observed ***[recall period]***, overall how would you rate the child's RSV symptoms now?' will be assigned to one of the 6 categories below:<br>□ None<br>□ Very mild<br>□ Mild<br>□ Moderate<br>□ Severe<br>□ Very severe |
| Status of health at each timepoint [categorical] | Each assessment of 'Overall, how is the child's health now?' will be assigned to one of the 6 categories below:<br>□ Excellent<br>□ Very good<br>□ Good<br>□ Fair<br>□ Poor<br>□ Very poor |
| Status of improvement of RSV symptoms at each timepoint [categorical] | Each assessment of 'Would you say the child's RSV symptoms have improved, are about the same or are worse than when the child entered the study?' will be assigned to one of the 5 categories below:<br>□ Very much improved<br>□ Much improved<br>□ A little improved<br>□ About the same<br>□ A little worse<br>□ Much worse<br>□ Very much worse |
| Time (hours) to improvement of RSV symptoms (based on general health question)<br><br>[time to event] | Time (in hours) from first dose of study drug until first date/time status of improvement of RSV symptoms reported as "very much improved" or "much improved" based on response to question 'Would you say the child's RSV symptoms have improved, are about the same or are worse than when the child entered the study?' collected at follow-up visits only.<br><br>Similar rules as for time to resolution of RSV symptoms (concepts) will be applied. |
| Status of return to pre-RSV disease health at each timepoint [binary] | Each assessment of 'Has the child's health returned to normal (how it was before RSV)?' will be assigned to one of the 2 categories below:<br>□ No<br>□ Yes |

**Table 17: Parameters based on PRESORS ObsRO**

| Measurement | Formula |
|---|---|
| Missing data: parent/caregiver PRESORS<br><br>[binary] | Missing parent/caregiver PRESORS: ObsRO assessments per day, from baseline to Day 21, will be identified per analysis visit window based on the data handling rules described in Section 2.1.4, specifically the assignment of worst assessment over a 24-hour period, as detailed in Table 6: Worst per Day where:<br>• Expected: number of **subjects** with expected assessments per day is based on the BID vs QD assessment schedule per protocol and for those subjects still ongoing in the study at the timepoint of interest (refer to Table 4: Planned Collection of PRESORS ClinRO, PRESORS ObsRO and Clinical Evaluation).<br>• Completed: number of **subjects** with completed (non-missing) assessments per day for those subjects still ongoing in the study at the timepoint of interest. Noting that during the BID assessment schedule, if at least one assessment is available for that day, it is regarded as sufficient, and subject is considered to have a completed assessment.<br>• Total missing: number of **subjects** with at least one missing assessment per day from baseline to Day 21. |
| Number of caregivers | Based on the number of raters per subject as indicated in the handheld eDevice. |

Refer to Section 5.4 for details regards parent/caregiver PRESORS ObsRO exploratory endpoints and analysis.

**PRESORS ClinRO:**

Based on collected data, the following are defined for analysis (refer to Table 18: Parameters based on PRESORS ClinRO):

**Table 18: Parameters based on PRESORS ClinRO**

| Measurement | Formula |
|---|---|
| ClinRO concept scores + change from baseline | Score per concept according to the score system provided in Attachment 3: PRESORS CLINRO Scoring System. Each concept score ranges from 0 to 3. The higher the score, the worse the symptom/concept. |
| ClinRO summary parameter scores + change from baseline | Average of the different concepts, ranging from 0 to 3.<br><br>Four summary parameters for which a summary score will be derived: key RSV symptoms, respiratory symptoms, general illness behavior and overall RSV symptoms and will be calculated as defined in Attachment 3: PRESORS CLINRO Scoring System. |
| ClinRO daily summary scores | For each ClinRO summary parameter (x4), a daily summary score will be derived utilizing the same two approaches to identify the worst concept score as described for PRESORS ObsRO (refer to Table 17 above):<br>**1. Average of the worst (PRIMARY APPROACH)**<br>**2. Worst of the average (SECONDARY APPROACH)** |

**Table 18: Parameters based on PRESORS ClinRO**

| | |
|---|---|
| | As exploratory analysis, this secondary approach will be evaluated versus the primary approach 'average of the worst'. |
| Status of overall condition at each timepoint [categorical] | Each assessment of 'Do you have any concerns relating to the subject's overall condition' will be assigned to one of the 3 categories below:<br>□ No concerns (condition is stable or improving)<br>□ Some concerns (may become unstable/requires close observation)<br>□ Extremely concerned (unstable, requires immediate medical review) |
| Status of health at each timepoint [categorical] | Each assessment of 'Overall, how would you rate the subject's current health status' will be assigned to one of the 4 categories below:<br>□ Excellent<br>□ Good<br>□ Fair<br>□ Poor |
| Health compared to the baseline assessment? [categorical] | ***Clinician's global rating of change (CGRC) question:***<br>With respect to the child's RSV infection, how would you describe the child's health now compared to the baseline assessment?<br><br>Ordinal scale from -5 to 5 where -5 indicates 'very much worse', 0 indicates 'unchanged', and 5 indicates 'very much better' |
| Missing data: clinician PRESORS<br><br>[binary] | Missing clinician PRESORS: ClinRO assessments per day, from baseline to Day 21, will be identified per analysis visit window based on the data handling rules described in Section 2.1.4, specifically the assignment of worst assessment over a 24-hour period, as detailed in Table 6: Worst per Day where:<br>• Expected: number of **subjects** with expected assessments per day is based on the BID vs QD assessment schedule per protocol, hospitalized vs outpatient status and for those subjects still ongoing in the study at the timepoint of interest (refer to Table 4: Planned Collection of PRESORS ClinRO, PRESORS ObsRO and Clinical Evaluation).<br>• Completed: number of **subjects** with completed (non-missing) assessments per day for those subjects still ongoing in the study at the timepoint of interest and taking into account subject status (hospitalized vs outpatient). Noting that during the BID assessment schedule, if at least one assessment is available for that day, it is regarded as sufficient, and subject is considered to have a completed assessment.<br>• Total missing: number of **subjects** with at least one missing assessment per day from baseline to Day 21. |
| Number of investigators | Based on the number of raters per subject as indicated in the handheld eDevice. |

Refer to Section 5.4 for details regards clinician PRESORS ClinRO exploratory endpoints and analysis.

#### 5.3.1.3. Other Clinical Course Parameters

##### 5.3.1.3.1. Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature

Formulae to be used for derived clinical course vital signs parameters, are provided in

Table 19.

**Table 19: Clinical Course Vital Signs Parameters**

| Measurement | Formula |
|---|---|
| Respiratory Rate (RR) actual values + changes from baseline | RR as measured by the investigator during scheduled visits<br>*change = (observed post-baseline RR – baseline RR)* |
| Heart Rate (HR) actual values + changes from baseline | HR as measured by the investigator during scheduled visits<br>*change = (observed post-baseline HR – baseline HR)* |
| Oxygen Saturation ($SpO_2$) actual values + changes from baseline | Oxygen Saturation as measured by the investigator during scheduled visits<br>*change = (observed post-baseline SpO2 – baseline SpO2)* |
| Body Temperature actual values + changes from baseline | Body Temperature: maximum body temperature considering all temperature assessments regardless of whether obtained during on-site visit or measured by caregiver and reported in handheld device<br>*change = (observed post-baseline temperature – baseline temperature)* |

### 5.3.1.3.2. Hospitalized Subjects only

Formulae to be used for derived clinical course parameters for the hospitalized subjects, are provided in Table 20.

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| Measurement | Formula |
|---|---|
| Time (hours) to hospital discharge [time to event] | The time from treatment initiation to first hospital discharge (=event) in hours.<br>Censoring will be done as follows:<br>**Situation** / **Censoring**<br>Missing information due to completion or withdrawal from study prior to the event: date of completion or withdrawal. If time is not available, the subject will be censored at 12:00.<br>Death (without previous discharge): date/time of death<br>*time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Time (hours) to clinical stability: investigator assessment<br>[time to event] | The time from treatment initiation to first clinical stability (=event) in hours, with clinical stability evaluated by the investigator and captured in the Clinical Stability eCRF.<br>*Censoring rules and derivation: as for 'Time (hours) to hospital discharge'* |
| Time (hours) to hospital discharge since hospital admission [time to event] | The time (hours) from hospital admission to first hospital discharge (=event) as captured in the Hospitalization (Inpatient) eCRF.<br>Derivation of censoring similar as "Time (hours) to hospital discharge". |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| | *time to event (hours) = (date/time of event or censoring – date/time of hospital admission)/3600, rounded to one decimal* |
| Time (hours) to clinical stability: investigator assessment since hospital admission [time to event] | The time (hours) from hospital admission to first clinical stability (=event), as evaluated by the investigator and captured in the Clinical Stability eCRF.<br>*Censoring rules and derivation: as for 'Time (hours) to hospital discharge'* |
| Duration of need for intensive care unit (ICU) stay (hours) [duration] | The total number of hours a subject experienced a **medical need** to stay in ICU (=event) from first dose of study drug until study termination, calculated as sum of [(end date/time of event – start date/time of event)/3600], rounded to one decimal for all separate events per subject as captured in the ICU eCRF. Based on the medical need to stay in ICU start/end date/time.<br>Where:<br>• If the initial start date/time is prior to the first dose of study drug, the duration prior to the first dose of study drug will be deducted from the overall duration<br>• If start date/time is missing, it will be imputed using date/time of first dose of study drug<br>• If the end date is missing, the end date is considered to be after study completion or withdrawal<br>• If the end date/time is after study completion/discontinuation, the duration after the date/time of study completion/discontinuation will be deducted from the overall duration (implies imputation of completion/discontinuation date/time)<br>• If start date is available but the start time is not available, it will be imputed as 00:00<br>• If end date is available but end time is not available and:<br>o End date equals hospital discharge date, end time will be imputed as the hospital discharge time (only if hospital discharge time is also not an imputed time), else imputed as 23:59 (if hospital discharge time is also an imputed time)<br>o End date does not equal hospital discharge date, end time will be imputed worst-case as 23:59 |
| Actual duration of intensive care unit (ICU) stay (hours)<br>[duration] | For subjects in Cohort 1: total number of hours of actual ICU stay experienced by a subject from first dose of study drug until end of study (sum of the duration of individual ICU records captured in the Hospitalization [Inpatient] eCRF) and is derived as:<br>*time hours = sum [(end date/time –start date/time [of encounter])]/3600*<br>*Derivation and imputation rules: as for 'Duration of need for intensive care unit (ICU) stay (hours)'* |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| Need for ICU stay<br>[binary] | Was there a **medical need** for the subject to stay in the ICU after first dose of study drug? Categories will be Yes (1) or No (0).<br>Only derive this parameter for subjects that were not in ICU before first dose of study drug (no score will be assigned otherwise). |
| Duration of oxygen supplementation<br>[duration] | The total number of hours a subject used supplemental oxygen (=event) from first dose of study drug until study termination, calculated as sum of [(end date/time of event - start date/time of event)/3600], rounded to one decimal for all separate events per subject<br>*Derivation and imputation rules: as for 'Duration of need for intensive care unit (ICU) stay (hours)'*<br>If the subject required oxygen supplementation prior to the current respiratory infection, the end date/time will be the date/time that the supplemental oxygen administration returned to the level provided prior to the current respiratory infection. |
| Need for oxygen supplementation<br>[binary] | Does the subject require any oxygen supplementation (non-invasive or invasive) after first dose of study drug?<br>Categories will be Yes (1) or No (0).<br>Only derive this parameter for subjects that did not require oxygen supplementation before first dose of study drug (no score will be assigned otherwise).<br>If the subject required supplemental oxygen prior to the current respiratory infection, requirement will be defined as having not returned to the level provided prior to the current respiratory infection. |
| Requirement for non-invasive non-mechanical ventilation support<br>[binary] | Does the subject require non-invasive non-mechanical ventilation support after first dose of study drug? On the Oxygen Supplementation form, oxygen supplementation is indicated but the type of supplemental oxygen administration does not equal "Non-Invasive Mechanical Ventilation" or "Invasive Mechanical Ventilation"?<br>Categories will be Yes (1) or No (0).<br>Only derive this parameter for subjects that did not require non-invasive non-mechanical ventilation before first dose of study drug (no score will be assigned otherwise). |
| Requirement for non-invasive mechanical ventilation support<br>[binary] | Does the subject require non-invasive mechanical ventilation support after first dose of study drug, as indicated on the Oxygen Supplementation form: type of supplemental oxygen administration equals "Non-Invasive Mechanical Ventilation"?<br>Categories will be Yes (1) or No (0).<br>Only derive this parameter for subjects that did not require non-invasive mechanical ventilation support or invasive mechanical |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| | ventilation support before first dose of study drug (no score will be assigned otherwise). |
| Requirement for invasive mechanical ventilation support<br><br>[binary] | Does the subject require invasive mechanical ventilation support after first dose of study drug, as indicated on the Oxygen Supplementation form: type of supplemental oxygen administration equals "Invasive Mechanical Ventilation"?<br><br>Categories will be Yes (1) or No (0).<br><br>Only derive this parameter for subjects that did not require invasive mechanical ventilation support before first dose of study drug (no score will be assigned otherwise). |
| Requirement for supplemental feeding/hydration<br><br>[binary] | Does the subject require supplemental feeding/hydration (e.g. IV catheter/nasogastric tube) after first dose of study drug?<br><br>Categories will be Yes (1) or No (0).<br><br>Only derive this parameter for subjects that didn't require supplemental feeding/hydration before first dose of study drug (no score will be assigned otherwise).<br><br>If the subject required supplemental feeding/hydration prior to the current respiratory infection, requirement will be defined as having not returned to the level provided prior to the current respiratory infection. |
| Duration of supplemental hydration/feeding (hours)<br><br>[duration] | Total number of hours of hydration/feeding support experienced from first dose of study drug until end of study (sum of the duration of individual hydration/feeding administration records captured in the Feeding/Supplemental Feeding eCRF) and is derived as:<br><br>*time hours = sum [(end date/time –start date/time [of encounter])]/3600*<br><br>*Derivation and imputation rules: as for 'Duration of need for intensive care unit (ICU) stay (hours)'* |
| Time (hours) to end of oxygen supplementation up to 72h from first hospital discharge<br><br>[time to event] | Regardless of whether or not the subject is receiving oxygen supplementation at time of first dose of study drug: time (hours) from first dose of study drug to last end date/time of any oxygen supplementation received, but within 72h following first hospital discharge. Excludes oxygen supplementation received during re-hospitalizations that occurred >72 hours after initial hospital discharge<br><br>Time (hours) will be set to 0h for subjects not requiring oxygen supplementation after first dose of study drug.<br><br>Censoring will be applied as follows:<br><br>**Situation** \| **Censoring** |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

<table>
<tr><td></td><td>
<table>
<tr><td>For subjects with missing data prior to event due to:<br>• Completion<br>• Withdrawal/early discontinuation of the study<br>• Lost to follow-up (LTFU)</td><td>Censored at date/time of completion, withdrawal/discontinuation of the study or LTFU accordingly<br>Note: missing time will be imputed as 12:00</td></tr>
<tr><td>Death (without previous evidence of supplementation end/hospital discharge)</td><td>Censored at date/time of death</td></tr>
</table>
<br>time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><td>Time (hours) to end of hydration/feeding supplementation up to 72h from first hospital discharge<br><br>[time to event]</td><td>Regardless of whether or not the subject is receiving hydration/feeding supplementation at time of first dose of study drug: time (hours) from first dose of study drug to last end date/time of any hydration/feeding supplementation received, but within 72h following first hospital discharge. Excludes hydration/feeding supplementation received during re-hospitalizations that occurred >72 hours after initial hospital discharge<br><br>Time (hours) will be set to 0h for subjects not requiring hydration/feeding supplementation after first dose of study drug.<br><br>Censoring will be applied as follows:
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>For subjects with missing data prior to event due to:<br>• Completion<br>• Withdrawal/early discontinuation of the study<br>• Lost to follow-up (LTFU)</td><td>Censored at date/time of completion, withdrawal/discontinuation of the study or LTFU accordingly<br>Note: missing time will be imputed as 12:00</td></tr>
<tr><td>Death (without previous evidence of supplementation end/hospital discharge)</td><td>Censored at date/time of death</td></tr>
</table>
<br>time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><td>Time (hours) to end of supplementation (oxygen and/or feeding/hydration) up to 72h from first hospital discharge<br><br>[time to event]</td><td>Time (hours) from first dose of study drug until the maximum date/time of supplementation end (oxygen- and/or hydration/feeding) and excluding supplementation received during re-hospitalizations that occurred >72 hours after initial hospital discharge.<br><br>Time (hours) will be set to 0h for subjects not requiring supplementation (oxygen- and/or hydration/feeding) after first dose of study drug.<br><br>In case either of the two components are censored, the time to actual end of supplementation (oxygen and/or hydration/feeding)</td></tr>
</table>

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| | will also be censored at the last timepoint of the censored component.<br><br>*time to event (hours) = (maximum (date/time of event or censoring) – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Time (hours) to return to pre-RSV disease level for RR: based on investigator evaluation<br><br>[time to event] | The time (hours) from first dose of study drug until the date/time to return to pre-RSV disease level. The return to pre-RSV disease level occurs when the observed value of the parameter is indicated by the investigator as normal, and no later observed values are indicated by the investigator as abnormal (=event).<br><br>Normalization of RR will be derived from the investigator response to the corresponding question in the Vital Signs eCRF: *'Is this RR value normal for this patient?'*<br><br>If no deterioration from pre-RSV disease levels occurred, the time will be set to time of first dose of study drug and the value will be set to 0 hours.<br><br>Subjects with an abnormal value at the last assessment will be censored at that time. Subjects for which this last assessment is the baseline assessment will be censored at time 0 hours.<br><br>*time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Time (hours) to return to pre-RSV disease level for HR: based on investigator evaluation<br><br>[time to event] | *Censoring rules and derivation: as for 'Time to return to pre-RSV disease level for RR: based on investigator evaluation''*<br><br>Normalization of HR will be derived from the investigator response to the corresponding question in the Vital Signs eCRF: *'Is this Pulse value normal for this patient?'* |
| Time (hours) to $SpO_2 \geq$ 92% on room air<br><br>[time to event] | The time from first dose of study drug until the time of first $SpO_2$ measurement $\geq$ 92% on room air, and where no supplemental oxygen supplementation is given at or after this timepoint and where no value < 92% are measured after this timepoint.<br><br>Subjects with $SpO_2$<92% on room air or who are still on oxygen supplementation at the last $SpO_2$ assessment will be censored at the date and time of the last $SpO_2$ assessment.<br><br>If no oxygen supplementation was necessary post-baseline and the subject had $SpO_2$ measurement $\geq$ 92% on room air at baseline and all post-baseline measurements, the value (time to event [hours]) will be set to 0 hours.<br><br>If the subject required supplemental oxygen prior to the current respiratory infection, end date/time will be defined as the date/time the subject has returned to the level provided prior to the current respiratory infection.<br><br>*time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal* |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| Time (hours) to $SpO_2 \geq$ 95% on room air<br><br>[time to event] | *Censoring rules and derivation: as for 'Time (hours) to $SpO_2 \geq 92\%$ on room air'* |
| Time (hours) to clinical stability: protocol definition<br><br>[time to event] | Time at which all the following criteria are met:<br><br>Return to pre-RSV disease status for otherwise healthy subjects and subjects with (a) risk factor(s) for severe RSV disease:<br>• heart rate AND<br>• respiratory rate AND<br>• blood oxygen level<br>AND<br>No more oxygen supplementation for otherwise healthy subjects and subjects with (a) risk factor(s) for severe RSV disease<br>AND<br>No more intravenous (IV)/nasogastric tube feeding/hydration in otherwise healthy subjects or return to pre-RSV status of IV/nasogastric tube feeding/hydration in subjects with (a) risk factor(s) for severe RSV disease<br><br>Time to clinical stability (protocol definition) will be evaluated using two approaches:<br><br>The time from first dose of study drug until the time at which each of the following criteria are met (=event):<br>• Normalization of oxygen supplementation (as in parameter Time [hours] to end of oxygen supplementation up to 72h from first hospital discharge),<br>• Normalization of feeding/hydration (as in parameter Time [hours] to end of hydration/feeding supplementation up to 72h from first hospital discharge),<br>• Normalization of RR (as in parameter Time [hours] to return to pre-RSV disease level for RR: based on investigator evaluation), and<br>• Normalization of HR (as in parameter Time [hours] to return to pre-RSV disease level for HR: based on investigator evaluation), and<br>• Normalization of blood oxygen level (as in parameter Time [hours] to $SpO_2 \geq 92\%$ on room air)<br><br>The time from first dose of study drug until the time at which each of the following criteria are met (=event): |

**Table 20: Additional Clinical Course Parameters for Hospitalized Subjects**

| | |
|---|---|
| | • Normalization of oxygen supplementation (as in parameter Time [hours] to end of oxygen supplementation up to 72h from first hospital discharge),<br>• Normalization of feeding/hydration (as in parameter Time [hours] to end of hydration/feeding supplementation up to 72h from first hospital discharge),<br>• Normalization of RR (as in parameter Time [hours] to return to pre-RSV disease level for RR: based on investigator evaluation), and<br>• Normalization of HR (as in parameter Time [hours] to return to pre-RSV disease level for HR: based on investigator evaluation), and<br>• Normalization of blood oxygen level (as in parameter Time [hours] to $SpO_2 \geq 95\%$ on room air)<br>In case any of the five components are censored, the time to clinical stability (protocol definition) will also be censored at the last timepoint of the censored component.<br>*time to event (hours) = (maximum (date/time of event criteria or censoring) – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Need for re-hospitalization<br>[categorical] | If, after being discharged from the hospital (initial hospital discharge), subject is re-hospitalized (ward or ICU [inpatient status]) due to respiratory or other reasons. Re-hospitalization status will be categorized as:<br>• Yes<br>  ○ Hospital admission date/time at least 24 hours after initial hospital discharge date/time AND<br>  ○ Reason for re-hospitalization, as assessed by the investigator, indicated on Medical Encounters [Inpatient/Outpatient] eCRF as:<br>  ▪ AE<br>  ▪ Other<br>If reason for re-hospitalization is indicated as AE, further differentiation will be made as follows:<br>• Respiratory AEs:<br>  – RSV-related complications: modified definition as detailed in Section 5.4<br>  – Other respiratory AEs<br>• Non-respiratory AEs<br>*This variable is only derived for those subjects who are re-hospitalized* |

#### 5.3.1.4. Acceptability and Palatability of the JNJ-53718678 formulation

Formula to be used for acceptability and palatability parameter is provided in Table 21.

**Table 21: Acceptability and Palatability Parameter**

| Measurement | Formula |
|---|---|
| Acceptability and palatability [categorical] | Assessment of 'In general, how did the child react when he/she was given the medicine? (note all that apply)'<br>□Child took medicine easily<br>□Disgusted expressions after tasting medicine<br>□Cried after tasting medicine<br>□Would not open mouth or turned head away to avoid medicine<br>□Spit out or coughed out medicine<br>□Gagged<br>□Vomited (within 2 minutes of swallowing medicine)<br><br>This is only captured once during visit Day 8 |
| Acceptability and palatability [binary] | Assessment of 'In general, how did the child react when he/she was given the medicine? (note all that apply)'<br><br>Categorized as 'Acceptable' (1) if answered:<br>□Child took medicine easily<br><br>Categorized as 'Partly or Not Acceptable' (0) in case any of the following responses were entered by the caregiver:<br>□Disgusted expressions after tasting medicine<br>□Cried after tasting medicine<br>□Would not open mouth or turned head away to avoid medicine<br>□Spit out or coughed out medicine<br>□Gagged<br>□Vomited (within 2 minutes of swallowing medicine)<br><br>This is only captured once during visit Day 8 |

#### 5.3.1.5. Medical Resource Utilization

Medical resource utilization will be assessed by the number, frequency and type of medical care encounters, including for RSV infection or RSV-related complications, based on investigator assessment.

Summary information will be provided as follows:

- Number of medical care encounters and reason (AE, Other)
- Type of medical care encounters such as medical practitioner office, emergency room, intensive care unit, home care, amongst others
- Type of practitioner
- Frequency of visits

## 5.3.2. Endpoint-specific analysis methods

### 5.3.2.1. RSV RNA Viral Load (qRT-PCR)

**$Log_{10}$ RSV RNA Viral Load**

Descriptive statistics mean (SE) graphs and median (IQR) graphs will be shown for the $log_{10}$ RSV RNA viral load actual values and changes from baseline by analysis visit and by treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 95% confidence interval, median, range and interquartile range. The aforementioned will be presented by the subgroups as defined in Section 2.4.

Differences on $log_{10}$ RSV RNA viral load by qRT-PCR between treatment groups and by analysis visit will be determined using appropriate contrasts in a similar mixed effects model as the one used for the primary efficacy endpoint (see Section 5.2.3). The 95% 2-sided confidence intervals will be presented.

**Association Between $Log_{10}$ RSV RNA Viral Load and Covariates/Baseline Indicators**

The potential association between the $log_{10}$ RSV RNA viral load and the following covariates and/or baseline indicators will be explored:

- Baseline $log_{10}$ RSV RNA viral load
- Presence/absence of risk factors for severe RSV disease
- Days since symptom onset (0,1,2,3,4,5)
- RSV subtype
- Medications of interest:
    - ♦ Any prior/concomitant use
    - ♦ No prior/concomitant use
- Supplemental oxygen at baseline
- Presence of other respiratory pathogens at baseline
- Presence of other respiratory viruses at baseline
- Age as collected at Screening (as continuous variable)
- Overall RSV symptoms summary score (ObsRO) at baseline
- Overall RSV symptoms summary score (ClinRO) at baseline
- Region [Class 2]
- Cohort [Class 1]
- Baseline neutrophils count (as continuous variable)

To predict the change in $log_{10}$ RSV RNA viral load over time at Day 3, Day 5 and Day 8 based on the aforementioned set of predictor variables (covariates and/or baseline indicators), multiple regression analysis using backward stepwise elimination, will be performed initially fitting all predictor variables to identify the prognostic factors. Then

factors are deleted one-by-one until a stopping condition is satisfied. At each step, the factor showing the smallest contribution to the model is eliminated. The parameter estimates along with the 95% 2-sided confidence limits by predictor variable will be produced. In addition, residual plots and goodness of fit measures will be evaluated, but not displayed in output. The SAS® procedure GLM SELECT (selection = backward SLS = 0.1) will be used. The procedure removes factors based on significance level and stops when all factors in the model are significant at the 0.1 level.

Predictor variables which show a strong association may further be explored as additional covariates in the primary efficacy model described in Section 5.2.3.

**RSV RNA Viral Load AUC**

A similar model as used for the primary analysis will be used for the RSV RNA viral load AUC until Day 3 and until Day 8. The differences in these AUCs for active versus placebo will be derived using appropriate contrasts for both Day 3 and Day 8 and from the same model containing all RSV RNA viral load assessments from baseline through Day 8.

Least squares mean estimates of the treatment differences, including the 95% 2-sided confidence intervals, will be presented.

For subgroup analyses, the model will also include subgroup variable as covariate, subgroup-by-treatment, subgroup-by-analysis visit and subgroup-by-analysis visit-by-treatment interactions. For details about subgroups refer to Section 2.4.

The individual AUCs until Day 14, derived using the trapezoidal method, will be analyzed using a generalized linear model with $AUC_{Day14/0\text{-}312h}$ as a dependent variable, treatment group and randomization stratification factors (derived) as fixed factors, and baseline $\log_{10}$ RSV RNA viral load as fixed covariate. The differences versus placebo will be estimated using appropriate contrasts and presented with 95% 2-sided confidence intervals.

**Proportion of Subjects with Undetectable RSV RNA Viral Load**

The proportion of subjects within the RSV RNA viral load categories (undetectable, detectable and quantifiable) will be shown in a frequency tabulation, as well as graphically, by treatment group and analysis visit. Subjects with missing data at that analysis visit will not be counted in the denominator for the proportion. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

Based on the binary categorization:

- Detectable or quantifiable = Yes (1)
- Undetectable = No (0)

the difference in proportion of undetectable between each active treatment group as compared to placebo will be investigated. Frequency procedure in SAS® provides Newcombe confidence limits with Mantel-Haenszel weights for the common risk difference, controlling for the two randomization stratification factors (separately). The

difference in proportion of undetectable and 95% 2-sided confidence interval for this point estimate, controlling for randomization stratification factors, will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Time to Virus Undetectable [time to event]**

With reference to the two time to event approaches, their definitions and derivations detailed in Section 5.3.1.1:

The time to event variables will be analyzed using Kaplan-Meier analysis (for both approaches). 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 95% 2-sided confidence intervals based on Kaplan-Meier transformation method, will be presented by treatment group. The data will be presented graphically using the Kaplan-Meier estimate of the survival function by treatment group.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4, for time (hours) to **confirmed undetectable** viral load only.

As sensitivity analysis, overall summary tables will be presented as described above for time (hours) to **confirmed undetectable** viral load but excluding nasal swab samples as previously described (refer to Section 5.2.3).

In addition to the Kaplan-Meier analysis, as described above, time (hours) to **confirmed undetectable** viral load and the differences in time to **confirmed undetectable** viral load of active dosing regimens versus placebo treatment, will also be estimated using the accelerated failure time (AFT) model, using the log-logistic distribution. The AFT model will include the categorical effects for treatment (with placebo as the reference), randomization stratification factors (derived) and baseline $\log_{10}$ RSV RNA viral load as continuous covariate. A summary of information from the final AFT model will include parameter estimates and associated standard errors and covariance matrix of parameter estimates, estimated accelerated failure time ratios versus placebo and associated 95% 2-sided confidence intervals.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

The parameter estimates and associated variance matrix resulting from AFT model, will be used in a generalized MCP-Mod approach that will test for existence of dose-response, at alpha=0.10 (1-sided). The aforementioned will be presented overall by treatment group only.

Graphical presentation will include:

- Overlay of survival curves with Kaplan-Meier survival function and AFT on one plot
- Forest plot of accelerated failure time ratios and resulting confidence intervals for subgroups of interest as defined in Section 2.4 including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

#### 5.3.2.2. Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS)

With reference to the definitions and derivations detailed in Section 5.3.1.2.1, the following will be presented.

**ObsRO Concept, Summary Parameter and Daily Scores; ClinRO Concept, Summary Parameter and Daily Scores**

Descriptive statistics will be shown for the actual values and changes from baseline by analysis visit and by treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 95% confidence interval, median, range and interquartile range. Descriptive statistics will be presented overall, and by subgroup (as defined in Section 2.4). For analyses for which we need at most one assessment per day (e.g. for summarizing combined in- and outpatient data captured by the clinician), we take the worst over 24 hours according to Table 6.

Graphical presentation of actual values and changes from baseline for individual concept scores and/or summary parameters (daily summary score [worst of the average]) over time will include:

- Mean (SE)
- BAR plots including:
  - Baseline PRESORS ObsRO/ClinRO
  - Subset of hospitalized subjects (Cohort 1): last PRESORS ObsRO/ClinRO concept scores BEFORE hospital discharge
  - Subset of hospitalized subjects (Cohort 1): first PRESORS ObsRO/ClinRO concept scores AFTER hospital discharge
- Individual subject profiles over time: key RSV symptoms

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

To explore the agreement between the two approaches (refer to Table 17 in Section 5.3.1.2.1), in identifying the worst concept score per day, used in deriving the four summary parameter daily summary scores, the actual values and changes from baseline summary scores over time will be presented graphically for each summary parameter individually (x4):

- Overlay of primary and secondary approach of Mean±SE daily summary scores over time on one plot:
  - **Average of the worst (PRIMARY APPROACH)**
  - **Worst of the average (SECONDARY APPROACH)**

The aforementioned will be presented overall by treatment group only.

**Association Between Summary Parameter Score: PRESORS ObsRO Key RSV Symptoms and Covariates/Baseline Indicators**

The potential association between the change from baseline in summary scores of the summary parameter, PRESORS ObsRO: key RSV symptoms and the covariates and/or baseline indicators of interest will be explored over time at Day X, Day 8 and Day 10 in a similar manner, utilizing multiple regression with backward stepwise elimination, as described for the RSV RNA viral load. Refer to Section 5.3.2.1 for details.

Day X is defined as the day when at least 50% of Cohort 1 subjects, across all treatment groups, have been discharged from hospital. The day identified will be used for both cohorts.

**PRESORS ObsRO: Change from Baseline: Mixed Model Repeated Measures**

For the summary parameter, PRESORS ObsRO: key RSV symptoms, change from baseline over time (average of the worst [primary approach] daily summary scores) will be analyzed using a restricted maximum likelihood based repeated measures approach. The analysis model will include fixed (discrete) effect parameters for treatment, randomization stratification factors (derived), analysis visit and treatment-by-analysis visit interaction, as well as continuous covariates for the baseline summary parameter score and baseline summary parameter score-by-analysis visit interaction. An unstructured covariance structure will be selected to model the within-subject errors. In case this model will not converge, the Toeplitz covariance structure will be applied. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Differences between treatment groups and by analysis visit will be determined using appropriate contrasts. Both the 80% and 95% 2-sided confidence intervals will be presented.

For subgroup analyses, the model will also include the subgroup variable as a covariate and the subgroup-by-treatment, subgroup-by-analysis visit and subgroup-by-analysis visit-by-treatment interactions. For details about subgroups refer to Section 2.4.

**Time to Resolution of Symptoms (Concepts) and Four Summary Parameters: Key RSV Symptoms, Respiratory Symptoms, General Illness Behavior and Overall RSV Symptoms (ObsRO)**

For the RSV symptoms (concepts) and four summary parameters, these time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided confidence intervals will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4, for summary parameters, key RSV symptoms and overall RSV symptoms only.

For time to resolution of summary parameters, key RSV symptoms and overall RSV symptoms (ObsRO), 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 resolved.

- 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.

These sensitivity analyses will be provided from IA#3 onwards.

In addition, for the summary parameters, key RSV symptoms and overall RSV symptoms, difference in median time (hours) to resolution (event) between each active treatment group as compared to placebo will be investigated using the AFT model with log-logistic distribution. The model will include class variables treatment group with placebo as reference and randomization stratification factors (derived) and baseline summary parameter score. Summary will include parameter estimates and associated standard error, covariance matrix of parameter estimates, estimated accelerated failure time ratio (as compared to placebo) and both 80% and 95% 2-sided confidence intervals.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

Parameter estimates and associated variance matrix resulting from AFT model, will be used in a generalized MCP-Mod approach to test dose-response, at 1-sided alpha level=0.10. The aforementioned MCP-Mod will be presented overall by treatment group only.

Graphical presentation will include:

- Overlay of survival curves with Kaplan-Meier survival function and AFT on one plot
- Forest plot of accelerated failure time ratios and resulting confidence intervals for subgroups of interest as defined in Section 2.4 including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

**Status of RSV Symptoms, Status of Health, Status of Improvement of RSV Symptoms, Status of Return to Pre-RSV Disease Health (ObsRO)**

The proportion of subjects within the categories will be shown in a frequency tabulation, as well as graphically, per analysis timepoint, per treatment group and analysis visit. Subjects with missing data at that analysis visit will not be counted in the denominator for the proportion. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Status of Overall Condition, Status of Health, Health Compared to the Baseline Assessment (ClinRO)**

The proportion of subjects within the categories will be summarized in a similar manner as described for aforementioned ObsRO ‘status’ variables.

**Missing Data: Caregiver/Clinician PRESORS, Number of Caregivers/Investigators**

Summary of the number (n) and percentage (%) of subjects with at least one completed assessment by analysis visit window (baseline to Day 21), for subjects still ongoing in the study at the timepoint of interest, will be presented overall by treatment group and cohort.

Total number of subjects with completed assessments from baseline to Day 21 will be evaluated relative to the total number of subjects with expected assessments taking into account the protocol-required assessment schedule.

Actual number of subjects with assessments missing per analysis visit window, taking into account the protocol-required assessment schedule and subject status (hospitalized vs outpatient) at the timepoint of interest, will also be presented.

The number of caregivers and investigators per subject, over the entire study course, will be presented as a frequency tabulation.

#### 5.3.2.3. Other Clinical Course Parameters

##### 5.3.2.3.1. Respiratory Rate, Heart Rate, Oxygen Saturation and Body Temperature

Descriptive statistics will be shown for the actual values and changes from baseline by visit and by treatment group. Descriptive statistics will include the number of subjects, mean, standard deviation, standard error, 95% confidence interval, median, range and interquartile range.

Graphical presentation of the Mean±SE of both actual values and changes from baseline vital signs over time will be provided.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

##### 5.3.2.3.2. Hospitalized Subjects only

**Time to Discharge, Time to Clinical Stability: Protocol Definition, Time to Clinical Stability: Investigator Assessment**

These time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided confidence intervals will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4

In addition, for time (hours) to hospital discharge (relative to date/time of first dose of study drug), the differences in median time of active dosing regimens versus placebo treatment will also be estimated using the AFT model. The AFT model will include the categorical effects for treatment (with placebo as the reference) and randomization stratification factors (derived). A summary of information from the final AFT model will include parameter estimates and associated standard errors and covariance matrix of parameter estimates, estimated accelerated failure time ratios versus placebo and the associated 80% and 95% 2-sided confidence intervals will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

The parameter estimates and associated variance matrix resulting from AFT model, will be used in a generalized MCP-Mod approach that will test for existence of dose-response, at alpha=0.10 (1-sided). The aforementioned MCP-Mod will be presented overall by treatment group only.

Graphical presentation will include:

- Overlay of survival curves with Kaplan-Meier survival function and AFT on one plot
- Forest plot of accelerated failure time ratios and resulting confidence intervals for subgroups of interest as defined in Section 2.4 including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

**Association Between Time (hours) to Hospital Discharge and Covariates/Baseline Indicators**

For Cohort 1 (hospitalized) subjects, the potential association between the time (hours) to hospital discharge (relative to date/time of first dose of study drug) and covariates/baseline indicators of interest, as detailed in Section 5.3.2.1, will be explored utilizing a similar AFT model as described above but including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

**RSV-related Re-hospitalization**

The proportion (number [n] and percentage [%]) of subjects will be presented as frequency tabulation:

- Re-hospitalized (any reason): percentage (%) based on total number of hospitalized subjects in ITT-i analysis set and treatment group
- Re-hospitalized:
  - Adverse event:
    - Respiratory AEs:
      - RSV-related complications: modified definition as detailed in Section 5.4
      - Other respiratory AEs
    - Non-respiratory AEs
  - Other

In addition, the main reason(s) for re-hospitalization will be summarized descriptively.

Individual subject profiles will be provided for all subjects re-hospitalized.

**Time to Discharge Since Hospital Admission, Time to Clinical Stability: Investigator Assessment Since Hospital Admission**

These time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided confidence intervals will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Need for ICU Stay, Need for Oxygen Supplementation, Requirement for Supplemental Feeding/Hydration**

With reference to the definitions and derivations detailed in Section 5.3.1.3.2, summary includes those subjects not requiring the level of care/support at date/time of first dose of study drug.

The proportion (number [n] and percentage [%]) of subjects with data available will be presented, as frequency tabulation, by treatment group. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

Based on the categorization (Yes vs No), the difference in proportions between each active treatment group as compared to placebo will be investigated. Frequency procedure in SAS® provides Newcombe confidence limits with Mantel-Haenszel weights for the common risk difference (difference in proportion), controlling for the two randomization stratification factors (separately). The difference in proportion of 'Yes' for any ICU/supplementation need and both 80% and 95% 2-sided confidence intervals for this point estimate, controlling for randomization stratification factors (derived), will be presented.

Derived duration will be summarized descriptively only.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Requirement for Non-invasive Non-mechanical Ventilation Support, Requirement for Non-invasive Mechanical Ventilation Support, Requirement for Invasive Mechanical Ventilation Support**

These need for/requirement parameters will be summarized in similar manner as described above and will only be calculated for those subjects that do not require ICU stay or supplemental support (depending on the parameter of interest) before the first dose of study drug.

**Time (hours) to End of Oxygen Supplementation, Time (hours) to End of Hydration/Feeding Supplementation, Time (hours) to End of Supplementation (up to 72h from first hospital discharge)**

These time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided confidence intervals will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

In addition, time (hours) to end of oxygen supplementation (up to 72h from first hospital discharge), difference in median time (hours) to event between each active treatment group as compared to placebo will be investigated using the AFT model with log-logistic distribution. The model will include class variables treatment group with placebo as reference and randomization stratification factors (derived). Summary will include parameter estimates and associated standard error, covariance matrix of parameter estimates, estimated accelerated failure time ratio (as compared to placebo) and both 80% and 95% 2-sided confidence intervals.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

Graphical presentation will include:

- Overlay of survival curves with Kaplan-Meier survival function and AFT on one plot

- Forest plot of accelerated failure time ratios and resulting confidence intervals for subgroups of interest as defined in Section 2.4 including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

**Time to Return to Pre-RSV Disease Level for Respiratory Rate, Time to Return to Pre-RSV Disease Level for Heart Rate, Time to SpO2≥92% on Room Air, Time to SpO2≥95% on Room Air**

These time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided CIs will be presented.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

#### 5.3.2.4. Acceptability and Palatability of the JNJ-53718678 formulation

For the individual categories, the proportion (number [n] and percentage [%]) of ITT-i subjects with data available at Day 8 will be presented, as frequency tabulation, by treatment group. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

As more than one response can be selected by the caregiver, subjects will be counted in each selected response such that the sum of percentages can be >100%.

Similar presentation based on the binary categorization will be provided.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

#### 5.3.2.5. Medical Resource Utilization

The proportion (number [n] and percentage [%] based on ITT-i analysis set) of subjects with any medical care encounters (Yes vs No) will be presented, as frequency tabulation, by treatment group. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

Based on the binary categorization, the difference in proportion of subjects with any medical care encounters (Yes) between each active treatment group as compared to placebo will be investigated. Frequency procedure in SAS® provides Newcombe confidence limits with Mantel-Haenszel weights for the common risk difference, controlling for the two randomization stratification factors (separately). The difference in proportion of 'Yes' for any medical care encounters and both 80% and 95% 2-sided confidence intervals for this point estimate, controlling for randomization stratification factors, will be presented.

Based on those subjects with medical care encounters, the following will be presented descriptively only:

- Reason for medical care encounters
- Type of medical care encounters
- Frequency of medical care encounters

- Type of practitioner

As subjects may have experienced one or more medical care encounters, subjects will be counted in each selected category such that the sum of percentages can be >100%.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

## 5.4. Exploratory Endpoints

Section 2.1.2 Endpoints of protocol, Amendment #6 (dated 01 December 2020), includes a detailed overview of efficacy and other endpoints (primary, secondary and exploratory) as planned per protocol. The exploratory efficacy endpoints listed below are additionally included, based on previous IAs with new information becoming available during the course of the study. These additional exploratory efficacy endpoints support decision-making for further development of JNJ-53718678 and interactions with health authorities.

Unless otherwise specified, the additional exploratory efficacy endpoints listed below, **will be analyzed and presented primarily for those subjects with symptom onset ≤3 days before randomization.**

**Parent/Caregiver PRESORS ObsRO**

- In hospitalized subjects (Cohort 1): RSV Recovery Scale (RRS): Day 1 to Day 8
- Time (hours) to resolution of RSV symptoms (concepts) and four summary parameters (ObsRO): 'supplemental-free' definition *(at least 24h oxygen- and hydration/feeding supplementation free)*

  *Note: aforementioned time (hours) to resolution ('supplemental free' definition) for both RSV concepts and summary parameters, developed during the course of the study based on new information available, is considered the primary definition of time (hours) to resolution for subsequent analyses. The addition of 'at least 24h supplementation free' requirement is to ensure that evaluation of time (hours) to resolution is an accurate reflection of the actual subject's resolution status rather than a time (hours) confounded by possible continued use of supplementation.*
- Potential association between the time (hours) to resolution of key- and overall RSV summary parameters (ObsRO ['supplemental-free' definition]) and covariates and/or baseline indicators of interest
- Time (hours) to resolution of key- and overall RSV summary parameters from hospital discharge (ObsRO): 'supplemental-free' definition *(at least 24h oxygen- and hydration/feeding supplementation free)*
- Resolved status per timepoint:
  - Day 1 to Day 8
  - BEFORE (last PRESORS ObsRO BEFORE)/AFTER (first PRESORS ObsRO AFTER) hospital discharge
- Sustained resolution of key- and overall RSV summary parameters
- AUC from immediately prior to first dose of study drug (baseline) through Day X ($AUC_{Day\ X}$), Day 8 ($AUC_{Day\ 8}$) and Day 10 ($AUC_{Day\ 10}$): key RSV symptoms

- Where Day X is defined as the day when at least 50% of Cohort 1 subjects, across all treatment groups, have been discharged from hospital.

**Clinician PRESORS ClinRO**

- In hospitalized subjects (Cohort 1): **clinically resolved** status (as composite endpoint): Day 1 to Day 8
- Resolved status per timepoint:
  - Day 1 to Day 8
  - BEFORE (last PRESORS ClinRO BEFORE)/AFTER (first PRESORS ClinRO AFTER) hospital discharge
- In hospitalized subjects (Cohort 1): time (hours) to resolution of the key RSV summary parameter (ClinRO): 'supplemental-free' definition *(at least 12h oxygen- and hydration/feeding supplementation free)*
- AUC from immediately prior to first dose of study drug (baseline) through Day X ($AUC_{Day\ X}$) and Day 8 ($AUC_{Day\ 8}$): key RSV symptoms

### 5.4.1. Definition

Relevant definitions and derivations pertaining to the aforementioned exploratory endpoints are specified in Table 22 below.

**Table 22: Exploratory Parameters**

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td colspan="2">PARENT/CAREGIVER PRESORS: ObsRO</td></tr>
<tr><td>RSV Recovery Scale (RRS): Day 1 to Day 8 [ordinal]</td><td>In hospitalized subjects: COHORT 1:<br>Study Day 1 to Day 8:<br>RRS is an ordinal scale assessing a subject's clinical status. Each category is based on data collected rather than asking the investigator to select the relevant category per subject, on each study day of assessment.<br><br>RRS provides 7 mutually exclusive conditions ordered from 'best to worst', and the analysis score reflects the subject's worst situation on the study day of assessment: Day 1 to Day 8:<br><br>
<table>
<tr><th colspan="2">RSV Recovery Scale (RRS)</th></tr>
<tr><th>Order</th><th>STATUS</th></tr>
<tr><td>1</td><td>Home Without Symptoms*</td></tr>
<tr><td>2</td><td>Home With Symptoms*</td></tr>
<tr><td>3</td><td>Ward, Not Requiring Supplementation (Feeding/Hydration and/or Oxygen Supplementation)</td></tr>
<tr><td>4</td><td>Ward), Requiring Supplementation(Feeding/Hydration and/or Oxygen Supplementation)</td></tr>
<tr><td>5</td><td>ICU, Not Requiring Mechanical Ventilation**</td></tr>
<tr><td>6</td><td>Requiring Mechanical Ventilation**</td></tr>
<tr><td>7</td><td>Death</td></tr>
</table>
*With or without symptoms is based on the key RSV symptoms (concepts): ObsRO and assessed as:<br>• Resolved: if ALL key RSV symptoms (concepts) scored as 0 (none) or 1 (mild) on study day of assessment OR</td></tr>
</table>

| Measurement | Formula |
|---|---|
| | • *Not resolved: if ANY of the key RSV symptoms (concepts) scored >1 on study day of assessment*<br>*Where the worst (highest) assessment collected per study day is considered.*<br>**Mechanical ventilation includes both invasive and non-invasive mechanical ventilation.<br><br>**RSV Recovery Scale: Definitions**<br>***Note:*** *hospital discharge status as based on investigator evaluation captured in the Inpatient/Outpatient Status- and/or Hospitalization [Inpatient] eCRFs*<br><br>**1. Home without symptoms:**<br>• Discharged from hospital prior to study day of assessment AND<br>• Without symptoms: based on the key RSV symptoms (concepts): ObsRO on study day of assessment<br><br>**2. Home with symptoms**<br>• Discharged from hospital prior to study day of assessment AND<br>• With symptoms: based on the key RSV symptoms (concepts): ObsRO on study day of assessment<br><br>**3. Ward, not requiring supplementation (feeding/hydration and/or oxygen supplementation)**<br>• In non-ICU (ward) on study day of assessment (including re-hospitalization as captured in Medical Encounters [Inpatient/Outpatient] eCRF) and neither supplemental oxygen nor supplemental hydration/feeding is required by subject<br><br>**4. Ward), requiring supplementation (feeding/hydration and/or oxygen supplementation)**<br>• In ward on study day of assessment (including re-hospitalization as captured in Medical Encounters [Inpatient/Outpatient] eCRF) and supplemental oxygen and/or supplemental hydration/feeding is required by subject<br><br>**5. ICU, not requiring mechanical ventilation**<br>• ICU level of care is required at any time during the study day of assessment AND<br>• Invasive or non-invasive mechanical ventilation not required by subject on study day of assessment<br><br>**6. Requiring mechanical ventilation**<br>• Any invasive or non-invasive mechanical ventilation on study day of assessment<br><br>**7. Death**<br>• Subject died prior to- or on study day of assessment (all-cause mortality)<br><br>**RSV Recovery Scale: ObsRO Imputation**<br>In case of missing ObsRO assessments following hospital discharge, the worst-case scenario of the two home categories of the RRS will be selected, i.e. 'Home with Symptoms' and imputed as subject's assessment of RRS for that study day. |
| Time (hours) to resolution of RSV *[summary* | Four summary parameters:<br>• Key RSV symptoms<br>• Respiratory symptoms |

| Measurement | Formula |
|---|---|
| *parameter]: 24h supplementation free definition*<br><br>[time to event] | • General illness behavior<br>• Overall RSV symptoms<br><br>In the subset of hospitalized subjects (Cohort 1), time (hours) from first dose of study drug until the date/time of first observed resolution of all individual RSV concepts comprising the relevant summary parameters (refer to Attachment 2 for concepts comprising each RSV summary parameter). *Where resolution occurs when ALL criteria, noted below, are met:*<br><br>• *All individua/ RSV concepts comprising relevant summary parameter are scored as 0 (none) or 1 (mild) for approximately 24h AND*<br>• *At least 24h oxygen supplementation free AND*<br>• *At least 24h hydration/feeding supplementation free)*<br><br>If caregiver is completing the ObsRO as expected per protocol, the approximate 24h summary score resolution can be defined with the considerations as detailed in Section 5.3.1.2.1.<br><br>In case not all RSV concepts, comprising a summary parameter, are resolved, data will be censored. Similar rules as for time to resolution of each ObsRO individual symptom (concept) will be applied as described in Section 5.3.1.2.1, such that:<br><br>*time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal* |
| Time (hours) to resolution of RSV *[summary parameter]* **from hospital discharge**<br><br>[time to event] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br><br>In the subset of hospitalized subjects (Cohort 1) 'not resolved' at date/time of hospital discharge as based on parent/caregiver PRESORS ObsRO: Time (hours) from hospital discharge until the date/time of first observed resolution of all individual RSV concepts comprising the relevant summary parameter (refer to Attachment 2 for concepts comprising each RSV summary parameter). *Where resolution is defined as a score of 0 (none) or 1 (mild) for approximately 24h.*<br><br>Utilizing the same derived variables as detailed in Section 5.3.1.2.1:<br><br>• Time (hours) to resolution<br>• Time (hours) to hospital discharge<br><br>*time to event (hours) = max(time to resolution [as defined above]) – time to hospital discharge), rounded to one decimal*<br><br>*For those subjects 'resolved' at date/time of hospital discharge, time (hours) is set to 0h.* |

| Measurement | Formula |
|---|---|
| Resolved status as based on PRESORS ObsRO: Day 1 to Day 8<br><br>[concepts] | For ObsRO symptoms (concepts): sleep disturbance, crying, illness behavior, breathing problems, retractions, tachypnea, breathing sounds, cough, nasal secretions, tachycardia, feeding, dehydration:<br>**Day 1 to Day 8:**<br>Resolved status per study day will be categorized as:<br>• RESOLVED: if individual RSV concept is scored as 0 (none) or 1 (mild)<br>• NOT RESOLVED: if individual RSV concept is scored >1<br>• MISSING: if no ObsRO assessment for given day (no imputation)<br>*Note: resolved status will be derived for each study day to Day 21, considering the worst (highest) assessment collected per study day, but is only presented from Day 1 to Day 8.* |
| Resolved status BEFORE/ AFTER HOSPITAL DISCHARGE as based on PRESORS ObsRO<br><br>[concepts] | **Hospital Discharge:**<br>In the subset of hospitalized subjects at time of hospital discharge: for each ObsRO concept, resolved status of the last ObsRO assessment BEFORE hospital discharge/first ObsRO assessment AFTER hospital discharge, will be categorized as described above. |
| Resolved status as based on PRESORS ObsRO: Day 1 to Day 8<br><br>[summary parameters] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br>**Day 1 to Day 8:**<br>Resolved status per study day will be categorized as:<br>• RESOLVED: if individual RSV concepts comprising the relevant summary parameter are all scored as 0 (none) or 1 (mild)<br>• NOT RESOLVED: if any of the individual RSV concepts comprising the relevant summary parameter are scored >1<br>• MISSING: if no ObsRO assessment for given day (no imputation)<br>*Note: resolved status will be derived for each study day to Day 21, considering the worst (highest) assessment collected per study day, but is only presented from Day 1 to Day 8.* |
| Resolved status BEFORE/ AFTER HOSPITAL DISCHARGE as based on PRESORS ObsRO<br><br>[summary parameters] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br>**Hospital Discharge:**<br>In hospitalized subjects at time of hospital discharge: for RSV summary parameters, resolved status of the last ObsRO assessment BEFORE hospital discharge/first ObsRO assessment AFTER hospital discharge, will be categorized as described above. |

| **Measurement** | **Formula** |
|---|---|
| Sustained resolution of RSV *[summary parameter]*<br><br>[categorical] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br><br>Sustained resolution, assessed over entire study course, is defined as no evidence of recurrence once resolution has been reached and where:<br>• Resolution is considered when *All individua/ RSV concepts comprising relevant summary parameter are scored as 0 (none) or 1 (mild) for approximately 24h (as in the definition of time [hours] to resolution).*<br>• Recurrence identified if any of the individual RSV concepts comprising the RSV summary parameter scored >1 = 'not resolved' following previous resolution.<br><br>Subjects will be evaluated over the course of the study and categorized ONCE as follows:<br>• Not Resolved: if, over entire study course, individual RSV concepts comprising the RSV summary parameter have not resolved<br>• Resolved With Recurrence: following resolution, individual RSV concepts comprising the RSV summary parameter >1 based on any of the subsequent ObsRO assessments<br>• Resolved Without Recurrence: once resolved, individual RSV concepts comprising the RSV summary parameter maintained at 0 (none) or 1 (mild) based on subsequent ObsRO assessments |

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><th colspan="2">CLINICIAN PRESORS: ClinRO</th></tr>
<tr><td><u>Clinically resolved</u> status as based on PRESORS ClinRO: Day 1 to Day 8<br><br>[categorical]</td><td>
In hospitalized subjects: COHORT 1:<br>
Day 1 to Day 8:<br>
Clinically resolved status, is a composite endpoint per study day of assessment: Day 1 to Day 8 and reflects subject's worst situation on the study day of assessment.<br><br>
A subject will be considered as clinically resolved on study day of assessment if, based on actual information collected, there is:<br>
• No oxygen supplementation<br>
• No supplemental hydration/feeding<br>
• No medical need of ICU<br>
AND<br>
• Resolution of key RSV symptoms based on PRESORS ClinRO ALL scored as 0 [none] or 1 [mild] on study day of assessment and considering the worst (highest) assessment collected on that day<br><br>
Since the PRESORS ClinRO is not assessed on a daily basis once a subject is discharged from the hospital (only assessed during follow-up visits to the site), imputation (based on the 'previous available-' and 'next available' PRESORS ClinRO assessment) will be applied if no PRESORS ClinRO available on a specific study day. Day 1 to Day 8 imputation is as follows:<br><br>
<table>
<tr><th>PREVIOUS Available PRESORS ClinRO</th><th>NEXT Available PRESORS ClinRO</th><th>Imputed Value</th><th>SENSITIVITY Analysis Imputed Value</th></tr>
<tr><td>Resolved</td><td>Resolved</td><td>Resolved</td><td>Resolved</td></tr>
<tr><td>Not resolved</td><td>Not resolved</td><td>Not resolved</td><td>Not resolved</td></tr>
<tr><td>Resolved</td><td>Not resolved</td><td>Not resolved</td><td>Not resolved</td></tr>
<tr><td>Not resolved</td><td>Resolved</td><td>Resolved</td><td>Not resolved</td></tr>
<tr><td>Resolved</td><td>Missing</td><td>Resolved</td><td>Resolved</td></tr>
<tr><td>Not resolved</td><td>Missing</td><td>Not resolved</td><td>Not resolved</td></tr>
<tr><td>Missing</td><td>Resolved</td><td>Resolved</td><td>Resolved</td></tr>
<tr><td>Missing</td><td>Not resolved</td><td>Not resolved</td><td>Not resolved</td></tr>
</table>
</td></tr>
<tr><td>Resolved status as based on PRESORS ClinRO: Day 1 to Day 8<br><br>[concepts]</td><td>
For ClinRO symptoms (concepts): activity level, sleep disturbance, retractions, tachypnea, breathing problems, feeding problems, cough, nasal secretions, wheezing, dehydration:<br>
Day 1 to Day 8:<br>
Resolved status per day will be categorized as:<br>
• RESOLVED: if individual RSV concept is scored as 0 (none) or 1 (mild)<br>
• NOT RESOLVED: if individual RSV concept is scored >1<br>
• MISSING: if no ClinRO assessment for given day (no imputation)
</td></tr>
</table>

| Measurement | Formula |
|---|---|
| | *Note: resolved status will be derived for each study day considering the worst (highest) assessment collected per study day.* |
| Resolved status BEFORE/ AFTER HOSPITAL DISCHARGE as based on PRESORS ClinRO<br><br>[concepts] | **Hospital Discharge:**<br>In the subset of hospitalized subjects at time of hospital discharge: for each ClinRO concept, resolved status of the last ClinRO assessment BEFORE hospital discharge/first ClinRO assessment AFTER hospital discharge, will be categorized as described above. |
| Resolved status as based on PRESORS ClinRO: Day 1 to Day 8<br><br>[summary parameters] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br><br>**Day 1 to Day 8:**<br>Resolved status per day will be categorized as:<br>• RESOLVED: if individual RSV concepts comprising the relevant summary parameter are all scored as 0 (none) or 1 (mild)<br>• NOT RESOLVED: if any of the individual RSV concepts comprising the relevant summary parameter are scored >1<br>• MISSING: if no ClinRO assessment for given day (no imputation)<br><br>*Note: resolved status will be derived for each study day considering the worst (highest) assessment collected per study day.* |
| Resolved status BEFORE/ AFTER HOSPITAL DISCHARGE as based on PRESORS ClinRO<br><br>[summary parameters] | RSV summary parameters:<br>• Key RSV symptoms<br>• Overall RSV symptoms<br><br>**Hospital Discharge:**<br>In hospitalized subjects at time of hospital discharge: for RSV summary parameters, resolved status of the last ClinRO assessment BEFORE hospital discharge/first ClinRO assessment AFTER hospital discharge, will be categorized as described above. |
| Time (hours) to resolution of RSV *[summary parameter]: 12h supplementation free definition*<br><br>[time to event] | For the summary parameter: key RSV symptoms considering ClinRO assessments during hospitalization only<br><br>In the subset of hospitalized subjects (Cohort 1), time (hours) from first dose of study drug until the date/time of first observed resolution of all individual RSV concepts comprising the relevant summary parameter (refer to Attachment 3 for concepts comprising each RSV summary parameter).<br><br>Where resolution is defined as:<br>• All individual RSV concepts comprising relevant summary parameter are scored as 0 (none) or 1 (mild)<br>• No oxygen- and/or hydration/feeding supplementation during previous 12 hours (as evaluated at the date/time of the ClinRO assessment) |

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
Confirmed resolution is defined as:
<ul>
<li>A second consecutive timepoint before hospital discharge, indicating resolution as defined above OR</li>
<li>Hospital discharge within 24 hours after the last ClinRO assessment before hospital discharge indicating resolution (as defined above)</li>
</ul>
This means that resolution can ONLY occur at the date/time of a ClinRO assessment. To illustrate:<br>
Step1: check ClinRO assessment for resolution of RSV concepts comprising the summary parameter<br>
Step 2: check if supplementation discontinued at least 12h prior to ClinRO assessment<br>
Step 3: if YES to the above, subject considered resolved at timepoint. If NO, check next ClinRO assessment and repeat the aforementioned steps.<br>
Step 4: check for confirmed response<br><br>
In case individual RSV concepts comprising the relevant summary parameter are not resolved, data will be censored as follows:
<table>
<tr><th>Situation</th><th>Censoring</th></tr>
<tr><td>Last record indicates resolution but insufficient recordings to meet the requirement of at least two consecutive assessments indicating resolution prior to hospital discharge and/or hospital discharge >24h after last assessment indicating resolution</td><td>Censored at date of last ClinRO assessment prior to hospital discharge</td></tr>
<tr><td>For subjects with missing data prior to hospital discharge (without previous resolution or evidence of hospital discharge) due to:<ul><li>Completion</li><li>Withdrawal/early discontinuation of the study</li><li>Lost to follow-up (LTFU)</li></ul></td><td>Censored at date/time of completion, withdrawal/discontinuation of the study or LTFU accordingly</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Measurement</th><th>Formula</th></tr>
<tr><td></td><td>
<table>
<tr><td>Assessment at last ClinRO before hospital discharge does not indicate resolution:<br>Derive:<br>x = end date/time of supplementation + 12h<br>y = hospital discharge date/time<br>z = time slot:<br>• 08:00 on the same day if the last ClinRO was a morning assessment (from 00:00 until 01:59)<br>• 20:00 on the same day if the ClinRO was a morning assessment (from 02:00 until 13:59)<br>• 8:00 the next day if the last ClinRO was an evening assessment (from 14:00 until 23:59)</td><td>• If x<y<z then censored at y<br>• If x<z<y then censored at z<br>• If y<x<z then censored at y<br>• If y<z<x then censored at y<br>• if z<x<y then censored at x<br>• if z<y<x then censored at z</td></tr>
<tr><td>Death (without previous resolution or hospital discharge)</td><td>Censored at date/time of death</td></tr>
</table>
<br>time to event (hours) = (date/time of event or censoring – date/time of first dose of study drug)/3600, rounded to one decimal</td></tr>
<tr><th colspan="2">OTHER CLINICAL COURSE ENDPOINTS</th></tr>
<tr><td>RSV-related complications: investigator assessment<br><br>[protocol definition]</td><td>Subjects who experienced a RSV-related complication after first dose of study drug will receive code 1, subjects who did not experience a complication will receive code 0.<br><br>The overall category will consist of any complication (answer to the question: “Is this AE a complication related to the current respiratory infection?”).<br><br>The following subcategories will also be analyzed:<br><br>▪ Respiratory complications, including<br>o Bacterial complications<br>o Viral complications<br>▪ Non-respiratory infectious complications, including<br>o Bacterial complications<br>o Viral complications<br>▪ Other<br><br>The RSV-related complication as per original definition will be provided as needed.</td></tr>
<tr><td>RSV-related complications: modified definition</td><td>Any subject who experienced at least one emergent adverse event included in the list of complications below will receive code 1, subjects who did not experience any of the specified emergent adverse events will receive code 0.</td></tr>
</table>

| Measurement | Formula |
|---|---|
| [study physician-identified complications] | • Respiratory complications: respiratory failure, respiratory distress, apneic attacks, bronchiolitis, bronchial obstruction, pneumonia, asthmatic crisis.<br>• Infectious complications: otitis media, bacterial respiratory tract infections, sepsis;<br>• Cardiovascular complications: arrhythmia, cardiogenic shock, hemodynamic instability, congestive cardiac failure;<br>• Acid-base or electrolyte complications: metabolic acidosis (serum $HCO_3^-$ <16), metabolic alkalosis (serum $HCO_3^-$ >30)<br>The final list of emergent adverse events to be considered as per modified definition of RSV-related complications, will be reviewed and documented prior to a database lock.<br><br>The modified definition for RSV-related complications will primarily be used as follows:<br><br>• from IA#3 and onwards<br>• in any decision rule that requires RSV-related complications data |
| Need for antibiotics related to complications associated with RSV: Investigator assessment<br><br>[categorical] | Need for antibiotics is defined as 'Yes' if the answers to the following 2 questions on the Adverse Events eCRF are answered with 'Yes' (Yes to both questions):<br><br>• Is this AE a complication related to the current respiratory infection?<br><br>• Concomitant or additional therapy given for this adverse event?<br><br>And if the answer to the following question on the Concomitant Medications eCRF for the related medication is answered with 'Yes'.<br><br>• Was this medication an Antibiotic? |

### 5.4.2. Analysis Methods

**PRESORS ObsRO: RSV Recovery Scale (RRS): Day 1 to Day 8**

The RRS will be assessed from Day 1 to Day 8. The proportion (number [n] and percentage [%]) of subjects per ordered categories will be presented, as frequency tabulation and graphically, by treatment group and study day.

The proportional odds model will be used to analyze the RRS Day 2 to Day 8, modeling the common odds ratio (cOR) of improvement on the ordinal scale of each active treatment group versus placebo. Ordered logistic regression model will include treatment group, baseline RRS category and the two randomization stratification factors (derived). The proportional odds model will be defined in such a way that a cOR <1 indicates larger improvement in the active treatment group.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Resolved Status Based on PRESORS ObsRO/ClinRO: Day 1 to Day 8, Resolved Status Based on PRESORS ObsRO/ClinRO Before/After Hospital Discharge**

Proportion (number [n] and percentage [%]) of subjects per individual categories will be presented graphically, by treatment group.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**PRESORS ClinRO: Clinically Resolved Status: Day 1 to Day 8**

Clinically resolved status, will be assessed from Day 1 to Day 8. The proportion (number [n] and percentage [%]) of subjects per individual categories will be presented, as frequency tabulation and graphically, by treatment group and study day.

A logistic regression model will be used to analyze the binary dependent variable, clinically resolved status Day 2 to Day 8, comparing each active treatment group versus placebo. Logistic regression model will include treatment group and the two randomization stratification factors (derived). Estimate of the treatment difference in proportion of clinically resolved status and both 80% and 95% 2-sided confidence intervals for this estimate will be obtained from the logistic regression model.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

A sensitivity analysis will be performed applying the alternative imputed value (Column 4: Sensitivity analysis imputed value [Section 5.4.1]).

**PRESORS ObsRO/ClinRO: Time to Resolution [Supplemental-free Definitions] and PRESORS ObsRO: Time to Resolution From Hospital Discharge**

For the RSV summary parameters specified in Section 5.4.1, these time to event variables will be analyzed using Kaplan-Meier analysis. Both the 80% and 95% 2-sided confidence intervals will be presented.

In addition, the RSV summary parameters will be further explored utilizing a similar AFT model as detailed for time (hours) to resolution in Section 5.3.2.2.

Graphical presentation will include:

- Overlay of survival curves with Kaplan-Meier survival function and AFT on one plot
- Forest plot of accelerated failure time ratios and resulting confidence intervals for subgroups of interest as defined in Section 2.4 including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Association Between PRESORS: ObsRO: Time (hours) to Resolution: 24h Supplementation Free Definition and Covariates/Baseline Indicators**

The potential association between the time (hours) to resolution: 24h supplementation free definition of summary parameter, PRESORS ObsRO: key RSV symptoms and covariates/baseline indicators of interest, as detailed in Section 5.3.2.1, will be explored utilizing a similar AFT model as described in Section 5.3.2.3.2, but including the relevant subgroup variable as covariate in the model with subgroup*treatment group interaction.

**PRESORS ObsRO: Sustained Resolution**

Proportion (number [n] and percentage [%]) of subjects per individual categories will be presented, as frequency tabulation and graphically, by treatment group. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories will be presented as based on the Wilson score test.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**PRESORS ObsRO/ClinRO: Key RSV Symptoms: AUC**

With reference to Section 5.2.3, a similar model as used for the primary efficacy analysis at Day 5 will be used for analysis of Day X ($AUC_{Day\ X}$), Day 8 ($AUC_{Day\ 8}$) and additionally for PRESORS ObsRO, Day 10 ($AUC_{Day\ 10}$). Where Day X is defined as the day when at least 50% of Cohort 1 subjects, across all treatment groups, have been discharged from hospital.

The difference between each active treatment group versus placebo will be derived using appropriate contrasts for Day X, Day 8 and Day 10 (PRESORS ObsRO only) from the same model containing all PRESORS ObsRO/ClinRO assessments from baseline through assessment day of interest (ObsRO: Day 10, ClinRO: Day 8).

The aforementioned will be presented for the subgroups as defined in Section 2.4.

**RSV-related Complications**

RSV-related complications will be provided based on the original (investigator assessment) and modified (study physician-identified complications) definitions.

**Original Definition (Investigator Assessment):**

The proportion of subjects with a complication (Yes and No) will be shown in a frequency tabulation including corresponding 95% CI by treatment as based on the Wilson score test.

Based on the binary categorization (Yes vs No), the difference in proportion of subjects with RSV-related complications, as assessed by the investigator, between each active treatment group as compared to placebo will be investigated. Frequency procedure in SAS® provides Newcombe confidence limits with Mantel-Haenszel weights for the common risk difference (difference in proportion of subjects with RSV-related complications), controlling for the two randomization stratification factors (separately). The difference in proportion of subjects with RSV-related complications and 80% and 95% 2-sided confidence intervals for this point estimate, controlling for randomization stratification factors, will be presented.

Similar frequency tables will be provided for the subcategories.

The aforementioned summary will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Modified Definition (Study Physician-identified Complications):**

The number (n) and percentage (%) of subjects in the ITT-i analysis set with RSV-related complications (Yes vs No) will be presented, as frequency tabulation. The incidence will

be presented for emergent adverse events (treatment phase and follow-up phase), as assessed by the study physician (modified definition), occurring during the study and treatment phase only.

The number (n) and percentage (%) of subjects, by MedDRA preferred term, in each of the subcategories will also be presented.

Based on the binary categorization (Yes vs No), the difference in proportion of subjects with RSV-related complications, modified definition, between each active treatment group as compared to placebo will be investigated and presented in a similar manner as described above.

The aforementioned summary will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

**Use of Antibiotics for RSV-related Complications: Investigator Assessment**

The proportion (number [n] and percentage [%]) of subjects using antibiotics for RSV-related complications at any time during the study (treatment phase and follow-up phase) will be presented, as frequency tabulation and graphically, by treatment group. Additionally, 95% 2-sided confidence interval for each binomial proportion within the individual categories (Yes vs No) will be presented as based on the Wilson score test.

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

## 5.5. Correlation Between Antiviral Effect and Clinical Course Endpoints

For each cohort separately, the relationship between primary antiviral effect endpoints and clinical course endpoints will be investigated.

***Cohort 1***

For antiviral effect endpoints:

- $Log_{10}$ RSV RNA viral load $AUC_{Day\ 5}$
- Time to **confirmed undetectable** RSV RNA viral load

For clinical course endpoints:

- PRESORS ObsRO summary parameters: key RSV symptoms and overall RSV symptoms:
  - Time (hours) to resolution (ObsRO): *24h supplementation free definition*
  - Change from Baseline in PRESORS ObsRO: key RSV symptoms and overall RSV symptoms at Day X, Day 8 and Day 10
    - Where Day X is defined as the day when at least 50% of Cohort 1 subjects, across all treatment groups, have been discharged from hospital.
- RSV-related complications (Yes vs No): modified definition
- RSV recovery scale (RRS) (ObsRO): Day 1 to Day 8
- Clinically resolved status (ClinRO): Day 1 to Day 8

- Time (hours) to hospital discharge from first dose of study drug
- Time (hours) to resolution of key RSV symptoms from hospital discharge
- Time to end of oxygen supplementation up to 72h from first hospital discharge
- Time to end of supplementation (oxygen and/or hydration/feeding) up to 72h from first hospital discharge

For each pair of variables (2 antiviral x 9 clinical course endpoints) and depending on data type (continuous vs categorical) the following will be used to explore the possible relationship:

- Spearman rank order correlation coefficients + scatterplots: evaluates the monotonic relationship between two continuous or ordinal variables. Ranges from -1 to 1 where 0 indicates no correlation.
- Box plots: graphically presents the association between continuous and binary variables.
- Kaplan-Meier survival curves: by binary category (if binary variable) or by quartiles of a continuous variable.
- Plot of $\log_{10}$ RSV RNA viral load vs summary parameter: key RSV symptoms (ObsRO) ("worst hourly" [refer to Table 6: Worst per Day and : Parameters based on PRESORS ObsRO]) daily summary score over time.

Similarly, for outpatients (Cohort 2) but including, at a minimum, the relevant clinical course endpoints as described below.

***Cohort 2***

For antiviral effect endpoints:

- $\text{Log}_{10}$ RSV RNAviral load $\text{AUC}_{\text{Day 5}}$
- Time to **confirmed undetectable** RSV RNA viral load

For clinical course endpoints, at a minimum the following will be explored:

- PRESORS ObsRO summary parameters: key RSV symptoms and overall RSV symptoms:
  - Time (hours) to resolution (ObsRO): *24h supplementation free definition*
  - Change from Baseline in PRESORS ObsRO: key RSV symptoms and overall RSV symptoms at Day X, Day 8 and Day 10
    - Where Day X is defined as the day when at least 50% of Cohort 1 subjects, across all treatment groups, have been discharged from hospital
- RSV-related complications (Yes vs No): modified definition

As new information becomes available, additional clinical course endpoints may be identified and explored utilizing the above methodology to ascertain possible relationships.

## 5.6. Decision Rules at Interim Analyses

During IAs, the primary viral load endpoint and 3 below-mentioned key clinical course endpoints are considered. Minimum acceptable value and target value for these key clinical course endpoints are defined in Table 23:

**Table 23: MAV and TV**

| Endpoint | Minimum Acceptable Value (MAV) | Target Value (TV) |
|---|---|---|
| Time to resolution of key RSV symptoms (ObsRO) | No difference (MAV = 0) | 1 day (24 hours) reduction (TV = -1) |
| Change from baseline (CFB) in summary parameter: key RSV symptoms (ObsRO) at Day 8 | No difference (MAV = 1) | 20% larger change from baseline, where the change from baseline represents a reduction in score (TV = 1.2*) |
| Incidence of RSV-related Complication | No difference (MAV = 0) | 10% absolute reduction in rate (TV = -0.1) |

* This represents a 20% increase in the magnitude of the CFB and not in the summary parameter score itself (i.e. if the CFB in the Placebo treatment group is -1.0, then the target CFB for the active treatment group would be -1.2)

Note that the viral load endpoint will be evaluated on a combined dataset of both cohorts for each interim analysis, except for IA#1 where only Cohort 1 data are available. Clinical course endpoints will be evaluated in the community cohort only for IA#3 and IA#4.

For IA#3 and IA#4 analyses, in case of severe imbalance between <=3 days and >3 days since symptom onset and where there are more subjects in the >3 to <=5 days stratum than in the <= 3 days stratum (i.e. >55% of subjects in the >3 to <=5 days stratum), a second analysis will be conducted considering 50% of subjects randomized in each stratum (symptom onset ≤ 3 days and symptom onset vs >3 to <=5 days) in each cohort separately. Chronological order of randomization (date and time) per stratum will be followed when defining the balanced dataset. In case there are inconsistencies in the results between the complete and the balanced analysis, no decision on altering the study (i.e. stopping for futility or enriching) will be taken and the study will proceed as planned and collect more data. In the case that a balanced analysis has been carried out (as described above), the sample size re-estimation at IA#3 will be performed on the balanced dataset only.
The IDMC will provide recommendations to the SC according to the below guidance:

**Interim Analysis 1**

The IDMC will review data on safety and tolerability, PK, and antiviral effect. Based on these data, the IDMC may make a recommendation to initiate enrollment in Cohort 2

**Interim Analysis 2**

The IDMC will consider stopping the study for futility if:

- The MCP-Mod trend test on viral load is non-significant at α=50% (1-sided), based on combined data from Cohort 1 and Cohort 2

AND

- At least one of the following criteria is true:
  - 95% 2-sided confidence interval on the difference in median time to resolution of key RSV symptoms between the high dose and placebo group excludes effects as good as the TV (i.e. lower limit of the confidence interval is above TV of '-1 day'), based on combined data from Cohort 1 and Cohort 2

OR

- 95% 2-sided confidence interval on the difference in median time to resolution of key RSV symptoms between the high dose and placebo group excludes effects as good as the TV (i.e. lower limit of the confidence interval is above TV of '-1 day'), based on data from Cohort 1 only

The above rule is considered non-binding. If the above pre-defined futility rule is hit, the SC will review available viral load and clinical course data, and might ask to perform subgroup analysis including, but not limited to, onset of symptoms and age group. Based on this, the SC may also consider enriching the population (i.e. limit future enrollment to subjects with ≤3 days since symptom onset), if there is evidence that the drug is not providing benefit to the subjects whose symptoms onset is >3 days.

**Interim analysis 3**

The IDMC will consider enriching the population (i.e. limit future enrollment to subjects with ≤3 days since symptom onset), if

- At least 2 out of 4 endpoints have conditional power <50%, where conditional power is defined as:
  - Viral load: conditional probability to reach success based on the MCP-Mod trend test at 1-sided alpha=2.5% at IA#4, based on combined data from Cohort 1 and Cohort 2.
  - Key clinical course endpoints: conditional probability of obtaining results in the "Go" region defined by a dual Go/No-Go framework at IA#4, based on data from Cohort 2 only.

The IDMC will review the re-calculation of the sample size using Cohort 2 data to limit the conditional probability of an inconclusive result to 20% on all clinical endpoints at the end of the study.

The IDMC will consider stopping the study for futility, if:

- The conditional power at IA#4 is <50% to demonstrate antiviral activity of JNJ-53718678 compared with placebo based on the MCP-Mod trend test on viral load at 1-sided alpha=2.5% based on combined data from Cohort 1 and Cohort 2.

AND

- 80% 2-sided confidence interval on at least 2 key clinical course endpoints excludes effects as good as the TV based on data from Cohort 2 only

AND

- None of the 80% 2-sided confidence intervals on any key clinical course endpoint excludes effects as bad as the MAV based on data from Cohort 2 only

For viral load, the conditional probability of success at IA#4 using combined data from Cohorts 1 and 2 will be calculated assuming i) no enrichment and ii) enrichment as described below.

In both cases, the conditional probability of success will be set to 1 if the 1-sided p-value for the MCP-Mod trend test is less than 2.5% at IA#3, as success has already been reached. Otherwise, the conditional Type I error will be calculated using the inverse-normal combination approach:

$$\rho = 1 - \Phi\left(\frac{\Phi^{-1}(0.975) - \sqrt{w_1}\Phi^{-1}(1 - p_{Full})}{\sqrt{1 - w_1}}\right)$$

where:

- $p_{Full}$ represents the 1-sided p-value for the MCP-Mod trend test for the full population at IA#3
- $w_1 = n_1 / n$
- $n_1$ represents the total number of randomized patients in Cohorts 1 and 2 at the time of IA#3
- $n = 294$, the planned total number of randomized patients in Cohorts 1 and 2 at IA#4

Given the conditional Type I error, the critical value for the MCP-Mod test based on new data from IA#4 only will be calculated. The conditional probability of success at IA#4 will be calculated under the observed test statistic at IA#3 ($Z_1$), adjusted for the sample size of the new data at IA#4 as:

$$CP_x = 1 - P\left(\cap_{i=1}^{3}\{Z_{i,2} \in (-\infty, CRV)\}\right)$$

where:

$$Z_2 \sim N\left(\mu_{Z,2} = \sqrt{\frac{n_2}{n_{1,x}}} Z_{1,x}\,, corr = corr_{MCPx}\right)$$

and:

- $x$ corresponds to the decision not to enrich / to enrich at IA#3
- $Z_{1,x}$represents the vector of observed MCP-Mod test statistics at IA#3 (Linear, Emax and Exponential models) based on the population of interest (full population for no enrichment and the sub-population with symptom onset ≤ 3 days for enrichment).
- $Z_2$ represents the vector of observed MCP-Mod test statistics for the second stage.
- $Z_{i,2}$ represents the observed MCP-Mod test statistic for the second stage (based on the new data at IA#4) for model i.
- $\mu_{Z,2}$ represents the vector of mean MCP-Mod test statistics for the second stage, which is estimated using the observed test statistics at IA#3.

- $n_{1,x}$ represents the number of randomized patients in Cohorts 1 and 2 at the time of IA#3 for the population of interest (full population for no enrichment and sub population for enrichment).

- $n_2$ represents the number of additional patients to be included in Cohorts 1 and 2 up until IA#4 (i.e. 294 - $n_{1,Full}$, where 294 is the total number of randomized subjects in Cohorts 1 and 2 at IA#4).

- $corr_{MCPx}$ represents the correlation matrix of the test statistics at IA#3 for the population of interest.

- *CRV* describes the critical value at IA#4, which is calculated based on the conditional 1-sided Type I error $\rho$, taking the multiplicity adjustment for MCP-Mod into account.

For the key clinical course endpoints, the conditional probabilities of obtaining results in the "Go", "Stop" and "Consider" regions at IA#4 and at the end of the study will be evaluated for Cohort 2 assuming i) no enrichment and ii) enrichment. Calculations of conditional power at IA#4 will assume a total sample size of 150 for Cohort 2 and calculations of conditional power at the end of the study will be calculated assuming total sample sizes for Cohort 2 of 150, 180, 210, 240, 270 and 300.

Analyses will be conducted as described below for each of the three key clinical course endpoints in order to estimate the following p-values at IA#3:

- $p_{Full;TV}$ and $p_{Sub;TV}$: 1-sided p-values to test the null hypothesis that the difference between the high dose and the placebo group is at least as good as the target value (TV) for the full and sub-populations against the alternative hypothesis that the difference between the high dose and the placebo group is worse than the TV.

- $p_{Full;MAV}$ and $p_{Sub;MAV}$: 1-sided p-values to test the null hypothesis that the difference between the high dose and the placebo group is no better than the minimum accepted value (MAV) for the full and sub-populations against the alternative hypothesis that the difference between the high dose and the placebo group is better than the MAV.

**Time to resolution of key RSV symptoms**

- The time to resolution of key RSV symptoms will be analyzed using an accelerated failure time (AFT) model, using the log-logistic distribution as described in Section 5.3.2.2. However, the term for baseline $\log_{10}$ viral load will be retained whether or not it is significant at the 10% significance level. The median time to resolution for the placebo group ($T_P$) in days will be estimated based upon this model and the TV that corresponds to a 1-day reduction for the high dose group will be calculated as a log relative reduction (i.e. as $\log[(T_P-1)/T_P]$). The MAV of no difference corresponds to a log relative reduction of $\log(T_P/T_P) = 0$. The 1-sided p-values for the tests to compare the difference between the high dose and placebo groups versus the TV and MAV will be derived using normal approximations for appropriate contrasts, $Z_{TV}$ and $Z_{MAV}$.

**Change from baseline in key RSV symptoms at Day 8**

- The change from baseline in key RSV symptoms at Day 8 will be analyzed using a restricted maximum likelihood repeated measures approach as described in Section

5.3.2.2. The adjusted mean reduction from baseline for the placebo group will be estimated based upon this model ($\overline{x_P}$) and the TV that corresponds to a 20% larger change from baseline for the high dose group (i.e. $1.2\overline{x_P}$) will be calculated. The MAV corresponds to a difference in the change from baseline of 0 (i.e. $1.0\overline{x_P}$). The 1-sided p-values for the tests to compare the difference between the high dose and placebo groups versus the TV and MAV will be derived using normal approximations for appropriate contrasts, $Z_{TV}$ and $Z_{MAV}$.

**Incidence of RSV-related complications**

- The 1-sided p-values to compare the proportion of subjects with at least one RSV-related complication between the high dose and placebo groups versus the MAV and TV will be derived using a normal approximation to the binomial distribution; where:

$$\hat{p}_1 - \hat{p}_2 \sim N\left(p_1 - p_2, \frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right)$$

The TV of an absolute reduction in rate of 10% corresponds to a difference in the proportion of subjects with at least one RSV-related complication in high dose versus placebo of -0.1. The MAV corresponds to a difference in the proportions of 0.

For each of the three clinical course endpoints, the conditional probability for the Stop decision for the situation without/with enrichment and for each assumed total sample size will be calculated as:

- $CP_{x;Stop} = 1 - \Phi\left(\frac{\Phi^{-1}(0.9) - \sqrt{w_1}\Phi^{-1}(1-p_{Full;TV})}{\sqrt{1-w_1}} - \sqrt{\frac{n_2}{n_{1,x}}}\Phi^{-1}(1-p_{x;TV})\right)$

The conditional probability for the Go decision for the time to resolution of key RSV symptoms and the incidence of RSV-related complications will be calculated as:

- $CP_{x;Go} = \Phi\left(min\{CRV_{TV} - \mu_{x;TV}, \mu_{x;MAV} - CRV_{MAV}\}\right)$

where:

- $CRV_{TV} = \frac{\Phi^{-1}(0.9) - \sqrt{w_1}\Phi^{-1}(1-p_{Full;TV})}{\sqrt{1-w_1}}$ and $CRV_{MAV} = \frac{\Phi^{-1}(0.9) - \sqrt{w_1}\Phi^{-1}(1-p_{Full;MAV})}{\sqrt{1-w_1}}$
- $\mu_{x;TV} = \sqrt{\frac{n_2}{n_{1,x}}}\Phi^{-1}(1-p_{x;TV})$ and $\mu_{x;MAV} = \sqrt{\frac{n_2}{n_{1,x}}}\Phi^{-1}(1-p_{x;MAV})$
- $x$ corresponds to the decision not to enrich / to enrich at #IA3
- $p_{x;TV}$ and $p_{x;MAV}$ represents p-values for the population of interest (full population for no enrichment and sub population for enrichment).
- $n_{1,x}$ represents the number of randomized patients in Cohort 2 at the time of IA#3 for the population of interest.

- $n_2$ represents the number of additional patients to be included in Cohort 2 up until the end of the study (i.e. N - $n_{1,Full}$, where N represents the total number of randomized subjects in Cohort 2 at the end of the study).

- $w_1 = n_1 / n_{Primary}$ where $n_{Primary} = 225$ is defined as midway between the planned sample size (N=150) and the maximum sample size (N=300) for Cohort 2.

The conditional probability of the Go decision for the change from baseline in key RSV symptoms at Day 8 needs to take the correlation, $\rho$, of $Z_{TV}$ and $Z_{MAV}$ into account.

$$\rho = -\frac{\left(\frac{1}{n_{H1,x}} + TV * MAV\frac{1}{n_{P1,x}}\right)}{\left(\sqrt{\frac{1}{n_{H1,x}} + TV^2/n_{P1,x}}\right)\left(\sqrt{\frac{1}{n_{H1,x}} + MAV^2/n_{P1,x}}\right)}$$

The conditional probability of the Go decision is calculated using a bivariate normal distribution where:

- $CP_{x;Go} = \mathrm{P}\left(Z_{x2;TV} < CRV_{TV} \cap Z_{x2;MAV} > CRV_{MAV};\ \mu = (\mu_{x;TV}, \mu_{x;MAV}), \rho\right)$

Where:

- $n_{H1,x}$ represents the number of Cohort 2 subjects in the high dose group that were included in the analysis at IA#3 for the population of interest.

- $n_{P1,x}$ represents the number of Cohort 2 subjects in the placebo treatment group that were included in the analysis at IA#3 for the population of interest.

- $Z_{x2;\,TV}$ represents the test statistic to test the null hypothesis that the difference between the high dose and the placebo treatment group is at least as good as the target value (TV) at the end of the study (full population for no enrichment and sub population with symptom onset ≤ 3 days for enrichment).

- $Z_{x2;\,MAV}$ represents the test statistic to test the null hypothesis that the difference between the high dose and the placebo treatment group is no better than the minimum acceptable value (MAV) at the end of the study (full population for no enrichment and sub population with symptom onset ≤ 3 days for enrichment).

For all clinical course endpoints, the conditional probability of an inconclusive result will then be calculated as:

$$CP_{x;Inconclusive} = 1 - CP_{x;Stop} - CP_{x;Go}$$

**Interim analysis 4**

The IDMC will consider stopping the study for futility, if:

- Viral load did not meet success based on the MCP-Mod trend test at 1-sided alpha=2.5% based on combined data from Cohort 1 and Cohort 2

AND

- 80% 2-sided confidence interval on at least 2 key clinical course endpoints excludes effects as good as the TV based on data from Cohort 2 only

AND

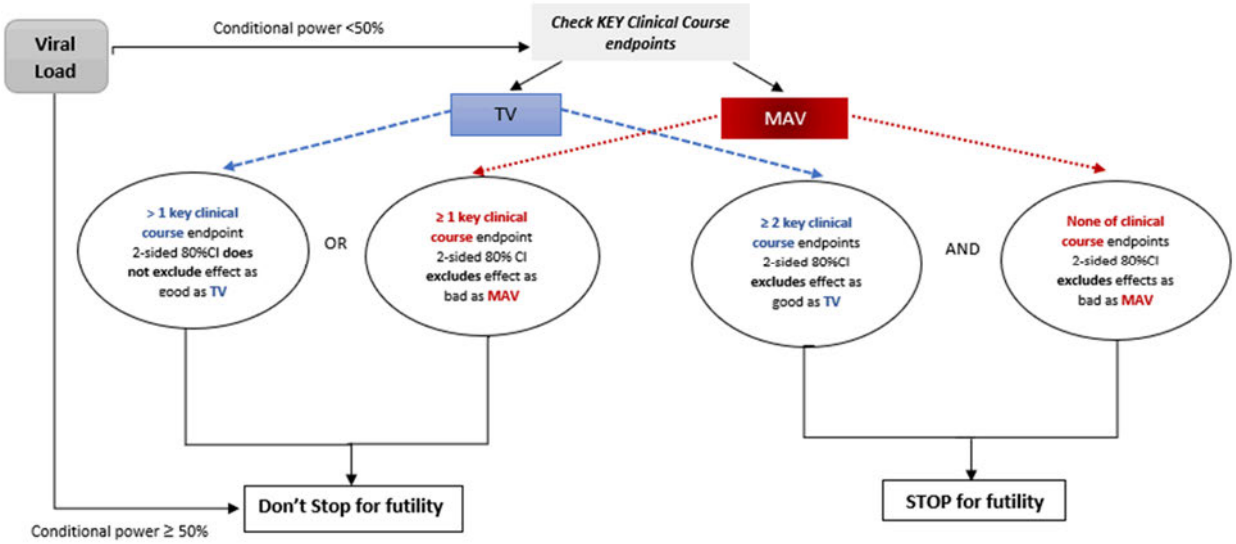
- None of the 80% 2-sided confidence intervals on any key clinical course endpoints excludes effects as bad as the MAV based on data from Cohort 2 only

For IA#3 and IA#4 two separate tests for two study populations are conducted and no formal multiplicity adjustments for the multiple study populations were implemented.

- Test for full population
- Test for subpopulation of patients ≤3 days since symptom onset

The futility rules defined are applied to each population separately. For decision-making, results of both populations will be considered. The following figure (refer to Figure 3: Decision Flowchart) provides an overview of the decision rules based on different endpoints to determine whether to stop the study for futility. Study will be stopped for futility if futility is reached in both populations.

**Figure 3: Decision Flowchart**




TV- Target value; MAV -Minimum Acceptable Value

## 6. SAFETY

All safety analyses will be descriptively summarized and based on the Safety analysis set. There will be no formal statistical testing for any safety endpoint. Refer to Section 2.4 for further details regards subgroup analysis, per the analyses detailed below.

## 6.1. Adverse Events

### 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.

Emergent AEs are categorized as related to study medication, if assessed, by the investigator, as 'possibly', 'probably', or 'very likely' related to the study medication.

**Phase Allocation of AE**

Adverse events present in the SDTM database are allocated to analysis phases based on their start date (refer to Section 2.1). If the start date of an event falls between (or on) the analysis phase start date and before- or on analysis phase stop date, the AE is attributed to that analysis 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. Adverse Events of Special Interest

In addition to RSV-related complications, detailed in Section 5.4, the following adverse events of special interest are defined (refer to Table 24: Cardiac Events Potentially Related to QT Prolongation):

**Table 24: Cardiac Events Potentially Related to QT Prolongation**

| MedDRA Preferred Term (PT) | MedDRA Code |
|---|---|
| Electrocardiogram QT interval abnormal | 10063748 |
| Electrocardiogram QT prolonged | 10014387 |
| Long QT syndrome | 10024803 |
| Long QT syndrome congenital | 10057926 |
| Torsade de pointes | 10044066 |
| Ventricular tachycardia | 10047302 |
| Cardiac arrest | 10007515 |
| Cardiac death | 10049993 |
| Cardiac fibrillation | 10061592 |
| Cardio-respiratory arrest | 10007617 |
| Electrocardiogram repolarisation abnormality | 10052464 |
| Electrocardiogram U wave inversion | 10062314 |
| Electrocardiogram U wave present | 10057913 |
| Electrocardiogram U-wave abnormality | 10055032 |
| Loss of consciousness | 10024855 |
| Electrocardiogram QT interval abnormal | 10063748 |
| Sudden cardiac death | 10049418 |
| Sudden death | 10042434 |
| Syncope | 10042772 |
| Ventricular arrhythmia | 10047281 |
| Ventricular fibrillation | 10047290 |
| Ventricular flutter | 10047294 |
| Ventricular tachyarrhythmia | 10065341 |

### 6.1.3. Analysis Methods

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 analysis phase (overall analysis treatment- and follow-up phase) and by analysis treatment phase only:

- any adverse events,
- serious adverse events,
- deaths due to AE (based on outcome = fatal),
- AEs at least Grade 3 or Grade 4 toxicity,
- AEs at least possibly related to study medication,
- AEs at least Grade 2 toxicity AND at least possibly related to study medication,
- AEs for which study medication was permanently stopped,
- AEs for which study medication was interrupted (action taken with study drug = drug interrupted),
- AEs for which study was discontinued prematurely,
- serious adverse events that were at least possibly related to study medication.

Aforementioned will be presented as an overview, overall and by each of the subgroups noted in Section 2.4. Presentation as incidence table or listing will depend on the number

of events identified, as detailed in a separate document (data presentation specifications [DPS]).

As part of safety, RSV-related complications during the overall analysis treatment- and follow-up phase, based on investigator's assessment, will be summarized descriptively. As RSV-related complications are analyzed as part of exploratory efficacy endpoints, refer to Section 5.4 for details regards analysis and presentation of RSV-related complications.

Emergent cardiac events potentially related to QT prolongation, identified based on MedDRA preferred term code, will be summarized descriptively by analysis phase (overall analysis treatment- and follow-up phase) and by analysis treatment phase only if there are at least 5 events identified across all treatment groups.

Listings will be provided for at least the following, depending on the number of events:

- All adverse events
- Serious adverse events
- AEs leading to death (based on outcome = fatal)
- Toxicity Grade 3 to 4 adverse events
- AEs for which study medication was permanently stopped
- AEs for which study medication was interrupted
- AEs for which study was discontinued prematurely

## 6.2. Clinical Laboratory Tests

### 6.2.1. Definitions

Laboratory parameters of hematology, serum chemistry, and urinalysis will be investigated. Analyses will be based on International System of Units (SI) converted values as available in the database.

**Toxicity grades and abnormalities for laboratory parameters**

The laboratory abnormalities will be determined according to the Division of Microbiology and Infectious Diseases (DMID) pediatric toxicity tables (see Attachment 1). Toxicity grades where available per parameter and age group, will be provided by the central laboratory and will be used in the analysis. In case no DMID toxicity grades are defined for a test and/or age group, 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 (analysis treatment, analysis follow-up [separately] and in combination analysis treatment + follow-up phase), including scheduled and 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.

For subjects enrolled under original protocol dated 13 July 2018, coagulation function will be monitored during this clinical study through evaluation of partial thromboplastin time (PTT) and activated partial thromboplastin time (aPTT) in seconds, and calculation of the International normalized ratio by the central lab. Grading of abnormalities in these parameters (PT and PTT) will be based on the DMID Pediatric Toxicity Table (see Attachment 1). Coagulation will not be evaluated in subjects enrolled as of protocol amendment 1 (dated 14 May 2019).

Post-amendment #4 (dated 26 May 2020), levels of potassium and magnesium will be determined by the central laboratory. In case of hypokalemia or hypomagnesemia at Screening or Day 8, the levels of potassium and magnesium are to be monitored locally and corrected to prevent cardiac disturbances. During the study locally determined potassium and/or magnesium levels need to be recorded in the eCRF as unscheduled laboratory visits/assessments. Data will be listed.

The eGFR will be calculated/reported by the central lab (Schwarz formula) and used as such in the analysis.

**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 emergence definition applies regardless of analysis phase and within each analysis phase.

**In case of missing date or partial dates**

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

Descriptive statistics (mean, standard deviation, median and range) will be provided for the clinical laboratory tests at each scheduled visit. Changes from baseline will be summarized by treatment group. Incidence of clinical laboratory tests that meet toxicity grades or criteria for abnormality will be tabulated for each treatment group.

A cross-tabulation of the worst toxicity/abnormality versus baseline toxicity/abnormality will be presented for the combination of analysis treatment- and follow-up phase and for analysis treatment phase only. This table will also show the number (n) and percentage (%) of subjects per worst toxicity/abnormality, the number (n) 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 change from baseline will be generated for all hematology and clinical chemistry tests by treatment group and by age group as assigned at Screening.

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

## 6.3. Vital Signs and Physical Examination Findings

### 6.3.1. Definitions

Systolic (SBP) and diastolic blood pressure (DBP), HR, RR, oxygen saturation and body temperature will be investigated. A directed physical examination (DPE) will be performed at several timepoints throughout the study, which includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination. Note that heart rate, respiratory rate, oxygen saturation ($SpO_2$) and body temperature are also analyzed as part of efficacy endpoints.

**Definitions Grades/Abnormalities**

Two sets of abnormality codes for SBP, DBP, HR, RR and oxygen saturation will be defined, as indicated in Table 25 and Table 26. Vital signs abnormalities will be identified based on subject's age at the time of the assessment and as follows:

- Worst grades/abnormalities are determined over the whole observational period and for each analysis phase separately, including post-baseline scheduled and unscheduled measurements of that analysis 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 25: Normal Ranges – Below/Normal (including extremes)/Above**

| Parameter (unit) | Age class | | | | |
|---|---|---|---|---|---|
| | 0 – 3 months | 3 – 6 months | 6 – 12 months | 1 – 2 years | 2- <3 years |
| Diastolic BP (mmHg) | 45 - 55 | 50 - 65 | 55 - 65 | 55 - 70 | 45 - 60 |
| Systolic BP (mmHg) | 65 -85 | 70 - 80 | 80 - 100 | 90 - 105 | 85 - 100 |
| Heart rate HR (bpm) | 100 - 150 | 90 - 120 | 80 - 120 | 70 - 110 | 95 - 125 |
| Respiratory rate | 35 - 55 | 30 - 45 | 25 - 40 | 20 - 30 | 22 - 30 |
| Oxygen saturation $SpO_2$ (%) | ≥96 | ≥96 | ≥96 | ≥96 | ≥96 |

**Table 26: Relevant Abnormalities – Abnormally Low/Normal/Abnormally High**

| Parameter (unit) | | Age class | | | |
|---|---|---|---|---|---|
| | | 0 – 3 months | 3 – 12 months | 1 - 2-years | 2- <3 years |
| Diastolic BP (mmHg) | abnormally low | <35 | <40 | <40 | <40 |
| | abnormally high | >65 | >85 | >90 | >70 |
| Systolic BP (mmHg) | abnormally low | <60 | <60 | <75 | <80 |
| | abnormally high | >110 | >110 | >120 | >110 |
| Heart rate HR (bpm) | abnormally low | <80 | <70 | <60 | <90 |
| | abnormally high | >180 | >150 | >140 | >130 |
| Respiratory rate | abnormally low | <25 | <20 | <18 | <20 |
| | abnormally high | >70 | >60 | >50 | >35 |
| Oxygen saturation $SpO_2$ (%) | abnormally low | <92 | <92 | <92 | <92 |

Abnormality codes for body temperature are defined, as indicated in Table 27.

**Table 27: Abnormalities for Body Temperature**

| Abnormality Code | Temperature (°C) | | | | |
|---|---|---|---|---|---|
| | Tympanic | Forehead | Oral | Rectal | Axillary |
| *Abnormalities on actual values* | | | | | |
| Normal | ≤ 37.8 | ≤ 38.0 | ≤ 38.0 | ≤ 37.2 | ≤ 38.0 |
| Abnormally high | > 37.8 | >38.0 | >38.0 | >37.2 | >38.0 |

**Emergence definition for grades/abnormalities**

A grade/abnormality will be considered emergent if it is worse than baseline. If baseline is missing, the grade/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 emergence definition applies regardless of analysis phase and within each analysis phase.

### 6.3.2. Analysis Methods

Descriptive statistics (mean, standard deviation, median and range) will be provided for the vital signs at each scheduled visit. Changes from baseline will be summarized by treatment group. Incidence of vital signs tests that meet criteria for abnormality will be tabulated for each treatment group.

A cross-tabulation of the worst grade/abnormality versus baseline will be presented for the combination of analysis treatment- and follow-up phase and for analysis treatment phase only. This table will also show the number (n) and percentage (%) of subjects per worst grade/abnormality, the number (n) and percentage (%) of subjects per emergent worst grade/abnormality. For Respiratory rate, heart rate and body temperature, the maximum value will be considered as the worst grade/value while for oxygen saturation, the lowest value will be considered the worst one. In determining the maximum body temperature, all temperature assessments will be considered regardless of whether obtained during on-site visit or measured by caregiver and reported in handheld device.

Mean±SE graphs over time for the actual values and changes from baseline will be generated and presented by treatment group and by age group as assigned at Screening.

A listing of abnormal individual subject vital signs values from scheduled and unscheduled timepoints will be provided. This listing will include all other timepoints 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 laboratory, they will not be recalculated. Overall interpretation will be based on the investigator's assessment as captured in the ECG eCRF and categorized as:

- Normal
- Abnormal
- Not evaluable

### 6.4.1. Definitions

**Definitions and Abnormalities**

The ECG abnormalities will be defined as indicated in Table 28. ECG abnormalities will be identified based on subject's age at the time of the assessment and as follows:

- Worst grades/abnormalities are determined over the whole observational period and for each analysis phase separately, including post-baseline scheduled and unscheduled measurements of that analysis 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 28: ECG Abnormalities**

| Parameter (unit) | Age class | Abnormally low | Abnormally high |
|---|---|---|---|
| PR (msec) | 0 - 2 years | NA | >150 |
| | 2 - <3 years | <100 | >150 |
| QRS (msec) | 0 - 2 years | NA | >79 |
| | 2 - <3 years | <40 | >79 |
| QT (msec) | 0 - 2 years | NA | >500 |
| | 2 - <18 years | <320 | >450 |
| RR (msec) | 0 - 3 months | <333 | >750 |
| | 3 - 12 months | <400 | >860 |
| | 1 - 2 years | <430 | >1000 |
| | 2 - <18 years | <600 | >1200 |
| **Abnormalities on the changes from baseline (ΔQTc)** | | | |
| | **Abnormality Code** | | **Criteria** |
| QT corrected | Borderline QTc change | | 30 ms < ΔQTc < 60 ms |
| | Abnormally high QTc change | | ΔQTc > 60 ms |
| **Abnormalities on actual QTcF values** | | | |
| QT corrected Fridericia's Correction Formula | Abnormally high QTcF value | | 450 ms < QTcF ≤ 480 ms<br>480 ms < QTcF ≤ 500 ms<br>>500 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' post-baseline (or vice versa) is also emergent. The emergence definition applies regardless of analysis phase and within each analysis phase.

**Triplicate ECG assessments**

If not available from the central ECG laboratory: for timepoints on which triplicate ECGs apply (expected for all timepoints), a mean value per triplet cluster, will be calculated per timepoint 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 have to be derived or any operations have to be performed (e.g. averaging over many assessments/triplicates), no rounding to the integer/unit will be performed; the maximum stored resolution of these derived values 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

Descriptive statistics (mean, standard deviation, median and range) will be provided for the ECG parameters at each scheduled visit. Changes from baseline will be summarized by treatment group. Incidence of ECG parameters that meet criteria for abnormality will be tabulated for each treatment group.

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

A tabulation of the worst QT/QTc change versus baseline per treatment for the combination of analysis treatment- and follow-up phase will be presented and for the analysis treatment phase only.

Mean±SE graphs over time for the actual values and changes from baseline will be generated and presented by treatment group and by age group as assigned at Screening.

A listing of abnormal individual subject ECG values from scheduled and unscheduled timepoints will be provided. This listing will include all other timepoints for the corresponding subject/parameter. In addition, ECG: Overall interpretation will also be listed.

# 7. VIROLOGY

## 7.1. Definitions

**Viral Strain Typing**

The RSV subtype is determined at baseline using the RSV A/B qRT-PCR assay performed in the central laboratory.

**Viral Sequencing**

Viral resistance will be evaluated by next-generation sequencing (NGS) of the RSV Fusion (F) gene using a read frequency cut-off of 3%.

Baseline samples from all subjects will be sequenced to identify pre-existing genetic variations 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 genetic variation**: amino acid difference from the RSV A or RSV B reference strain detected at baseline with an NGS-read frequency ≥15%.

- **Emerging genetic variation:** a genetic variation (amino acid substitution, insertion or deletion) that is absent, i.e. an NGS-read frequency <3%, at baseline but detected with an NGS-read frequency ≥15% at a later post-baseline timepoint.
- **Enriched genetic variation**: a genetic variation (amino acid substitution, insertion or deletion) that is present at baseline with an NGS-read frequency ≥3% and <15%, but with an increase in NGS-read frequency of at least 15% post-baseline.
- **Genetic variation profile**: a specific genetic variation or combination of genetic variations at one or more timepoints.
- **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 24 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, as well as residues involved in binding of JNJ-53718678 to the RSV pre-fusion F protein: positions 127, 137, 138, 140, 141, 143, 144, 323, 338, 339, 392, 394, 396, 397, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517.

**Analysis Timepoints**

Virology results will be assigned to the visit windows as described in Sections 2.1.1 and 2.1.4. In addition to the timepoints corresponding to the visits at which samples for RSV F gene sequencing are collected, the below timepoints will be considered:

- Baseline: closest timepoint with sequencing data available prior to the first dose of study drug. Ideally, this will be the Day 1 pre-dose 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 Timepoint: last available post-baseline timepoint during the study treatment phase with sequencing data available. In case no On-Treatment assessment is available, the first assessment during study follow-up phase will be selected.
- Any Post-baseline Timepoint During the Study: all available post-baseline timepoints in the study with sequencing data available.

## 7.2. Analysis Methods

### 7.2.1. Viral Sequencing

Subjects with baseline RSV A+B co-infection will be excluded from the summary tables.

**Baseline**

The prevalence of baseline genetic variations in the RSV F gene (complete RSV F gene or considering the positions of interest), i.e. the number of subjects with baseline genetic variations in the RSV F gene, will be tabulated in frequency outputs (n, %).

**Post-baseline**

Emerging and enriched genetic variations in the RSV F gene (complete RSV F gene or considering the positions of interest) will be tabulated by analysis timepoint in frequency outputs (n, %).

Over the study period, amino acid changes from reference sequence at baseline and post-baseline will be listed for all subjects using an NGS-read frequency cut-off of 3%. For subjects with emerging or enriched genetic variations, RSV RNA viral load profiles including emerging or enriched genetic variations per timepoint, will be generated. Subgroup analyses by the presence of baseline genetic variations or emerging genetic variations will be tabulated to evaluate the impact on response (i.e. $AUC_{Day\ 5}$ and time to **confirmed undetectable** RSV RNA viral load).

The aforementioned will be presented overall by treatment group and by the subgroups as defined in Section 2.4.

# 8. IMPACT OF PANDEMIC

With the onset of the global 2019 novel coronavirus (COVID-19) pandemic, impact on planned analyses is to be considered in accordance with regulatory guidance. Taking into consideration the study status, impact to subject safety, data quality and integrity is considered minimal.
With reference to the current version of the COVID-19 standard reporting – guiding principles, the following will be evaluated for COVID-19 impact and may be presented in a separate listing:

- Protocol deviations: deviations due to COVID-19 and can be considered major or minor.
- Treatment and study disposition: premature discontinuation of treatment/study due to COVID-19.
- Visit/assessment schedule: missed visits/assessments due to COVID-19.
- Adverse events: COVID-19 associated adverse events and deaths.

## REFERENCES

(1) Pinheiro, J., Bornkamp, B. Glimm, E. and Bretz, F. (2013), Model based Dose-Finding under model-uncertainty using general parametric models. Statistics in Medicine. 33. 10.

# ATTACHMENTS

## ATTACHMENT 1: DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES (NOVEMBER 2007; DRAFT)

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID)**
**PEDIATRIC TOXICITY TABLES NOVEMBER 2007**
**DRAFT**

**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 or death*: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable |

* The draft DMID pediatric toxicity tables characterize death as a Grade 5 event, for the purposes of this study the sponsor will categorize events into 4 grades and has included death with life-threatening in the Grade 4 category.

**SERIOUS OR LIFE-THREATENING ADVERSE EVENTS**

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 WHO) have been adapted for use by the 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.

## DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

**(Selected Values for children less than or equal to 3 months of age – does not apply to preterm infants)**

**For all parameters not listed in this table, please refer to the DMID Toxicity Table for children >3 months of age**

| **HEMATOLOGY** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Hemoglobin** | | | | |
| 1-7 days old | 13.0-14.0 g/dL | 12.0-12.9 g/dL | <12 g/dL | Cardiac Failure secondary to Anemia |
| 8-21 days old | 12.0-13.0 g/dL | 10.0-11.9 g/dL | <10.0 g/dL | Cardiac Failure secondary to Anemia |
| 22-35 days old | 9.5-10.5 g/dL | 8.0-9.4 g/dL | <8.0 g/dL | Cardiac Failure secondary to Anemia |
| 36-60 days old | 8.5-9.4 g/dL | 7.0-8.4 g/dL | <7.0 g/dL | Cardiac Failure secondary to Anemia |
| 61-90 days old | 9.0-9.9 g/dL | 7.0-8.9 g/dL | <7.0 g/dL | Cardiac Failure secondary to Anemia |
| **Absolute Neutrophil Count** | | | | |
| 1 day old | 5000-7000/$mm^3$ | 3000-4999/$mm^3$ | 1500-2999/$mm^3$ | <1500/$mm^3$ |
| 2-6 days old | 1750-2500/$mm^3$ | 1250-1749/$mm^3$ | 750-1249/$mm^3$ | <750/$mm^3$ |
| 7-60 days old | 1200-1800/$mm^3$ | 900-1199/$mm^3$ | 500-899/$mm^3$ | <500/$mm^3$ |
| 61-90 days old | 750-1200/$mm^3$ | 400-749/$mm^3$ | 250-399/$mm^3$ | <250/$mm^3$ |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Selected values for children younger than or aged 3 months)**

| **HEMATOLOGY (continued)** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Bilirubin** (fractionated bilirubin test must be performed when total bilirubin is elevated) | | | | |
| <7 days old | - | 20-25mg/dL | 26-30 mg/dL | >30 mg/dL |
| 7-60 days old | 1.1-1.9xN | 2.0-2.9xN | 3.0-7.5xN | >7.5xN |
| 61-90 days old | 1.1-1.9xN | 2.0-2.9xN | 3.0-7.5xN | >7.5xN |
| **Creatinine** | | | | |
| <7 days old | 1.0-1.7 mg/dL | 1.8-2.4 mg/dL | 2.5-3.0 mg/dL | >3.0 mg/dL |
| 7-60 days old | 0.5-0.9 mg/dL | 1.0-1.4 mg/dL | 1.5-2.0 mg/dL | >2.0 mg/dL |
| 61-90 days old | 0.6-0.8 mg/dL | 0.9-1.1 mg/dL | 1.2-1.5 mg/dL | >1.5 mg/dL |
| **Creatinine Clearance** | | | | |
| <7 days old | 35-40 mL/min | 30-34 mL/min | 25-29 mL/min | <25 mL/min |
| 7-60 days old | 45-50 mL/min | 40-44 mL/min | 35-39 mL/min | <35 mL/min |
| 61-90 days old | 60-75 mL/min | 50-59 mL/min | 35-49 mL/min | <35 mL/min |
| **Hypocalcemia** | | | | |
| <7 days old | 6.5-6.9 mEq/L | 6.0-6.4 mEq/L | 5.5-5.9 mEq/L | <5.5 mEq/L |
| 7-60 days old | 7.6-8.0 mEq/L | 7.0-7.5 mEq/L | 6.0-6.9 mEq/L | <6.0 mEq/L |
| 61-90 days old | 7.8-8.4 mEq/L | 7.0-7.7 mEq/L | 6.0-6.9 mEq/L | <6.0 mEq/L |
| **Hypercalcemia** | | | | |
| <7 days old | 12.0-12.4 mEq/L | 12.5-12.9 mEq/L | 13.0-13.5 mEq/L | >13.5 mEq/L |
| 7-60 days old | 10.5-11.2 mEq/L | 11.3-11.9 mEq/L | 12.0-13.0 mEq/L | >13.0 mEq/L |
| 61-90 days old | 10.5-11.2 mEq/L | 11.3-11.9 mEq/L | 12.0-13.0 mEq/L | >13.0 mEq/L |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **LOCAL REACTIONS** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Induration | <10 mm | 10-25 mm | 26-50 mm | >50 mm |
| Erythema | <10 mm | 10-25 mm | 26-50 mm | >50 mm |
| Edema | <10 mm | 10-25 mm | 26-50 mm | >50 mm |
| Rash at Injection Site | <10 mm | 10-25 mm | 26-50 mm | >50 mm |
| Pruritus | Slight itching at injection site | Moderate itching at injection extremity | Itching at injection extremity and other sites | Itching over entire body |

| **HEMATOLOGY** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Hemoglobin for children older than 3 months and younger than 2 years of age | 9.0 - 9.9 g/dL | 7.0 - 8.9 g/dL | <7.0 g/dL | Cardiac Failure secondary to anemia |
| Hemoglobin for children older than 2 years of age | 10 - 10.9 g/dL | 7.0 - 9.9 g/dL | <7.0 g/dL | Cardiac Failure secondary to anemia |
| Absolute Neutrophil Count | 750 - 1200/$mm^3$ | 400 - 749/$mm^3$ | 250 - 399/$mm^3$ | <250/$mm^3$ |
| Platelets | ------- | 50,000 - 75,000/$mm^3$ | 25,000 - 49,999/$mm^3$ | <25,000/$mm^3$ |
| Prothrombin Time (PT) | 1.1 - 1.2 x ULN | 1.3 - 1.5 x ULN | 1.6 - 3.0 x ULN | >3.0 x ULN |
| Partial Thromboplastin Time (PTT) | 1.1 - 1.6 x ULN | 1.7 - 2.3 x ULN | 2.4 - 3.0 x ULN | >3.0 x ULN |

## DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

### (Older than 3 months of age)

| **GASTROINTESTINAL** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Bilirubin (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 |
| Bilirubin (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 |

| | | | | |
|---|---|---|---|---|
| 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 |
| Pancreatic Amylase | 1.1 - 1.4 x ULN | 1.5 - 1.9 x ULN | 2.0 - 3.0 x ULN | >3.0 x ULN |
| Uric Acid | 7.5 - 9.9 mg/dL | 10 - 12.4 mg/dL | 12.5 - 15.0 mg/dL | >15.0 mg/dL |
| CPK | See Neuromuscular Toxicity | | | |
| Appetite | - | Decreased appetite | Appetite very decreased, no solid food taken | No solid or liquid taken |
| Abdominal Pain | Mild | Moderate- No Treatment Needed | Moderate- Treatment Needed | Severe- Hospitalized for treatment |
| Diarrhea | Slight change in consistency and/or frequency of stools | Liquid stools | Liquid stools greater that 4x the amount or number normal for this child | Liquid stools greater than 8x the amount or number normal for this child |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **GASTROINTESTINAL (continued)** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Constipation | Slight change in the consistency/frequency of stool | Hard, dry stools with a change in frequency | Abdominal pain | Distention and Vomiting |
| Nausea | Mild | Moderate- Decreased oral intake | Severe-Little oral intake | Unable to ingest food or fluid for more than 24 hours |
| Vomiting | 1 episode/day | 2-3 episodes per day | 4-6 episodes per day | Greater than 6 episodes per day or Intractable Vomiting |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **ELECTROLYTES** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **CREATININE** | | | | |
| 3 months - 2 years of age | 0.6 - 0.8 x ULN | 0.9 - 1.1 x ULN | 1.2 - 1.5 x ULN | >1.5 x ULN |
| 2 years - 12 years of age | 0.7 - 1.0 x ULN | 1.1 - 1.6 x ULN | 1.7 - 2.0 x ULN | >2.0 x ULN |
| Older than 12 years of age | 1.0 - 1.7 x ULN | 1.8 - 2.4 x ULN | 2.5 - 3.5 x ULN | >3.5 x ULN |
| Hypernatremia | - | <145 - 149 mEq/L | 150 - 155 mEq/L | >155 mEq/L or abnormal sodium AND mental status changes |
| Hyponatremia | - | 130 - 135 mEq/L | 129 - 124 mEq/L | <124 mEq/L or abnormal sodium AND mental status changes |
| Hyperkalemia | 5.0 - 5.9 mEq/L | 6.0 - 6.4 mEq/L | 6.5 - 7.0 mEq/L | >7.0 mEq/L or abnormal potassium AND cardiac arrhythmia |
| Hypokalemia | 3.0-3-5 mEq/L | 2.5-2.9 mEq/L | 2.0-2.4 mEq/L | <2.0 mEq/L or abnormal potassium AND cardiac arrhythmia |
| Hypercalcemia | 10.5 - 11.2mg/dL | 11.3 - 11.9 mg/dL | 12.0 - 12.9 mg/dL | >13.0 mg/dL |
| Hypocalcemia | 7.8 - 8.4 mg/dL | 7.0 - 7.7 mg/dL | 6.0 - 6.9 mg/dL | <6.0 mg/dL |
| Hypomagnesemia | 1.2 - 1.4 mEq/L | 0.9 - 1.1 mEq/L | 0.6 - 0.8 mEq/L | <0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia |
| Hypoglycemia | 55 - 65 mg/dL | 40 - 54 mg/dL | 30 - 39 mg/dL | <30 mg/dL or abnormal glucose AND mental status changes |
| Hyperglycemia | 116 - 159 mg/dL | 160 - 249 mg/dL | 250 - 400 mg/dL | >400 mg/dL or ketoacidosis |
| Proteinuria | Tr-1+ or <150 mg/day | 2+ or 150-499 mg/day | 3+ or 500-1000 mg/day | 4+ or Nephrotic syndrome >1000 mg/day |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **ELECTROLYTES (continued)** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Hematuria | Microscopic <25 cells/hpf | Microscopic >25 cells/hpf | ---- | Gross hematuria |
| Hypernatremia | - | <145 - 149 mEq/L | 150 - 155 mEq/L | >155 mEq/L or abnormal sodium AND mental status changes |
| Hyponatremia | - | 130 - 135 mEq/L | 129 - 124 mEq/L | <124 mEq/L or abnormal sodium AND mental status changes |
| Hyperkalemia | 5.0 - 5.9 mEq/L | 6.0 - 6.4 mEq/L | 6.5 - 7.0 mEq/L | >7.0 mEq/L or abnormal potassium AND cardiac arrhythmia |
| Hypokalemia | 3.0 – 3.5 mEq/L | 2.5 - 2.9 mEq/L | 2.0 - 2.4 mEq/L | <2.0 mEq/L or abnormal potassium AND cardiac arrhythmia |
| Hypercalcemia | 10.5 - 11.2mg/dL | 11.3 - 11.9 mg/dL | 12.0 - 12.9 mg/dL | >13.0 mg/dL |
| Hypocalcemia | 7.8 - 8.4 mg/dL | 7.0 - 7.7 mg/dL | 6.0 - 6.9 mg/dL | <6.0 mg/dL |
| Hypomagnesemia | 1.2 - 1.4 mEq/L | 0.9 - 1.1 mEq/L | 0.6 - 0.8 mEq/L | <0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia |
| Hypoglycemia | 55 - 65 mg/dL | 40 - 54 mg/dL | 30 - 39 mg/dL | <30 mg/dL or abnormal glucose AND mental status changes |
| Hyperglycemia | 116 - 159 mg/dL | 160 - 249 mg/dL | 250 - 400 mg/dL | >400 mg/dL or ketoacidosis |
| Proteinuria | Tr-1+ or <150 mg/day | 2+ or 150-499 mg/day | 3+ or 500-1000 mg/day | 4+ or Nephrotic syndrome >1000 mg/day |
| Hematuria | Microscopic <25 cells/hpf | Microscopic >25 cells/hpf | - | Gross hematuria |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **CENTRAL NERVOUS SYSTEM (CNS)** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Generalized CNS Symptoms | - | - | Dizziness | Hypotonic, hyporesponsive episodes; Seizures; Apnea/Bradycardia; Inconsolable crying >3 hrs; |
| Headache | Mild | Moderate, Responds to non-narcotic analgesia | Moderate to Severe, Responds to narcotic analgesia | Intractable |
| Level of Activity | - | Slightly irritable OR slightly subdued | Very irritable OR Lethargic | Inconsolable OR Obtunded |
| Visual | - | Blurriness, diplopia, or horizontal nystagmus of <1 hour duration, with spontaneous resolution | More than 1 episode of Grade 2 symptoms per week, or an episode of Grade 2 symptoms lasting more than 1 hour with spontaneous resolution by 4 hours or vertical nystagmus | Decrease in visual acuity, visual field deficit, or oculogyric crisis |
| Myelopathy | - | None | None | Myelopathic/spinal cord symptoms, such as: pyramidal tract weakness and disinhibition, sensory level, loss of proprioception, bladder/bowel dysfunction |

**DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007**

**(Older than 3 months of age)**

| **PERIPHERAL NERVOUS SYSTEM** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |

| | | | | |
|---|---|---|---|---|
| Neuropathy/ Lower Motor Neuropathy | - | Mild transient Paresthesia only | Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss | Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness. |
| Myopathy or Neuromuscular Junction Impairment | Normal or mild (<2 x ULN) CPK elevation | Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN) | Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN; | Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms |

## DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) PEDIATRIC TOXICITY TABLES NOVEMBER 2007

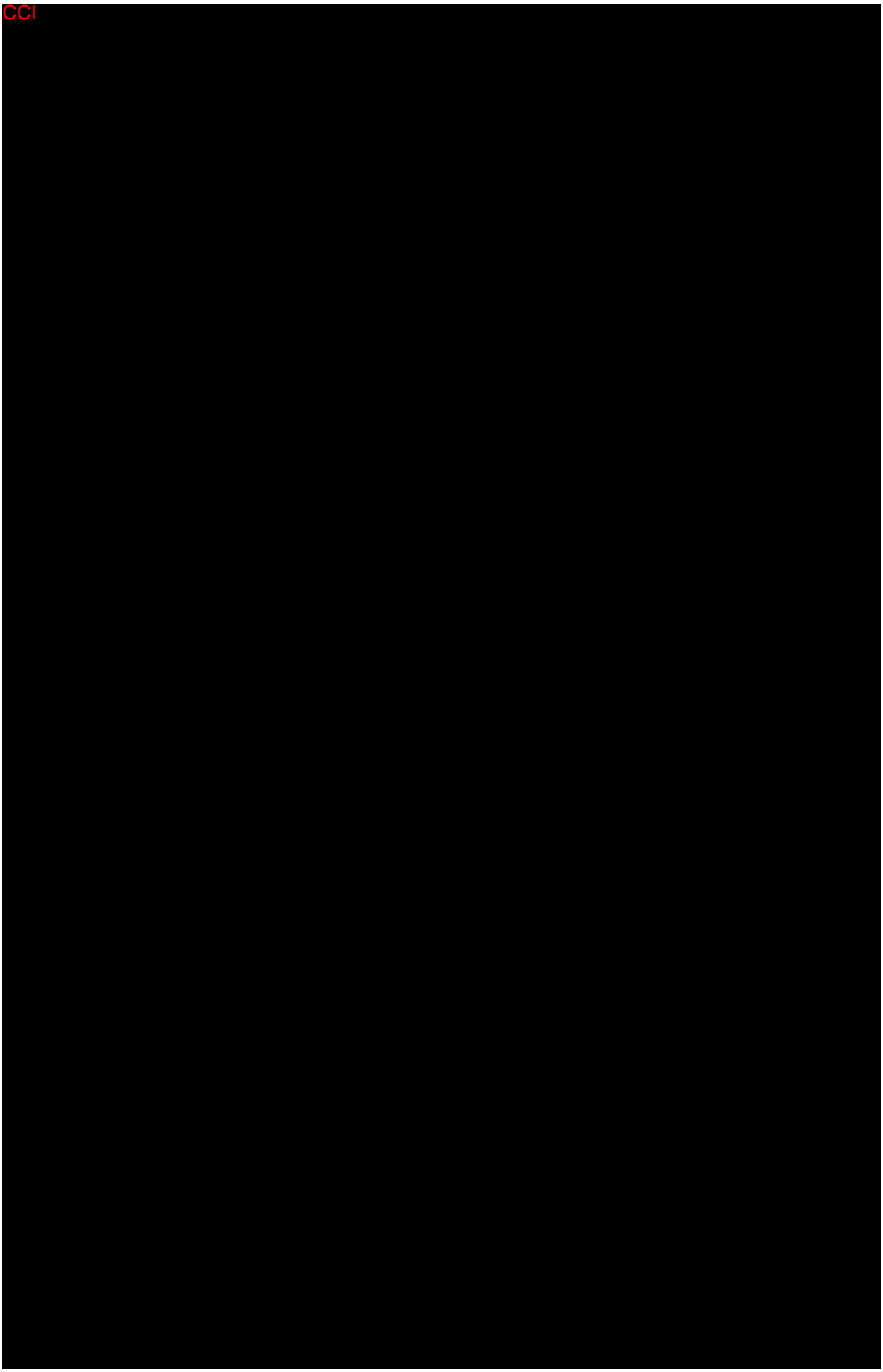
### (Older than 3 months of age)

| **OTHER** | | | | |
|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Allergy | Pruritus without Rash | Pruritic Rash | Mild Urticaria | Severe Urticaria Anaphylaxis, Angioedema |
| Drug Fever (Rectal) | - | 38.5 - 40.0°C 101.3 – 104.0 °F | Greater than 40.0°C Greater than 104.0°F | Sustained Fever: Equal or greater than 40.0°C (104.0°F) for longer than 5 days |
| Cutaneous | Localized rash | Diffuse maculopapular Rash | Generalized urticaria | Stevens-Johnson Syndrome or Erythema multiforme |

| | | | | |
|---|---|---|---|---|
| Stomatitis | Mild discomfort | Painful, difficulty swallowing, but able to eat and drink | Painful: unable to swallow solids | Painful: unable to swallow liquids; requires IV fluids |
| Clinical symptoms *not otherwise specified* in this table | No therapy; monitor condition | May require minimal intervention and monitoring | Requires medical care and possible hospitalization | Requires active medical intervention, hospitalization, or hospice care |
| Laboratory values *not otherwise specified* in this table | Abnormal, but requiring no immediate intervention; follow | Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug | Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug | Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug |

## ATTACHMENT 2: PRESORS OBSRO SCORING SYSTEM

CCI



CCI

[redacted]

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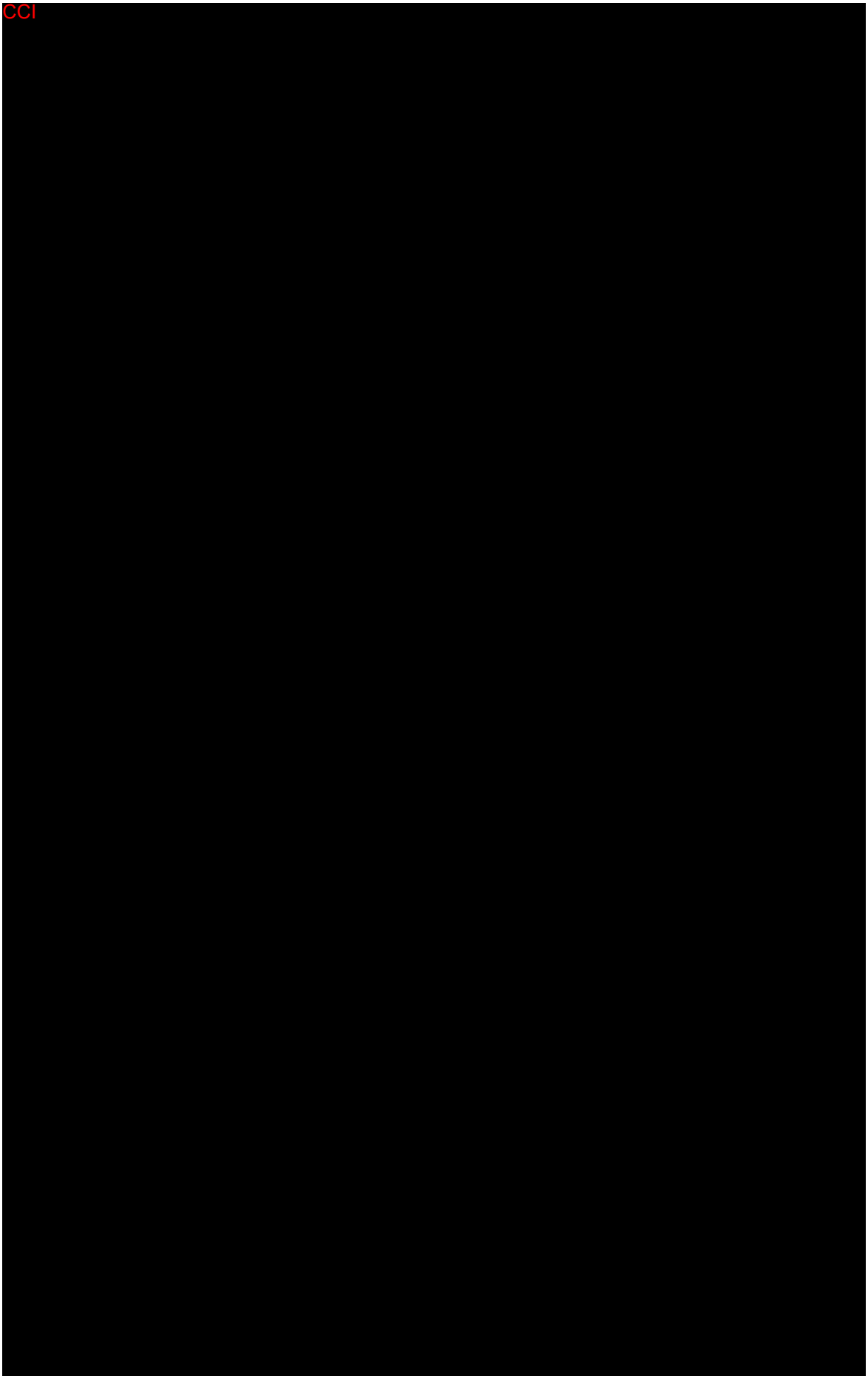
CCI

## ATTACHMENT 3: PRESORS CLINRO SCORING SYSTEM

CCI



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