Janssen Research & Development*

Clinical Protocol

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
AMENDMENT 6

JNJ-53718678

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

EudraCT NUMBER: 2016-003642-93

Status: Approved
Date: 1 December 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-ERI-127967555, 17.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	13 Jul 2018
Amendment 1	14 May 2019
Amendment 2	5 Jul 2019
Amendment 3	20 Dec 2019
Amendment 4	26 May 2020
Amendment 5	10 Jul 2020
Amendment 6	01 Dec 2020

Amendments are listed beginning with the most recent amendment.

Amendment 6 (01 December 2020)

The overall reason for the amendment: The overall rationale for the changes implemented in the protocol amendment is to maximize enrollment of subjects with at least moderate RSV disease severity, where potentially greater treatment benefit can be achieved.

Applicable Section(s)	Description of Change(s)
	Rationale: Inclusion Criterion 4 was changed to maximize enrollment of subjects with at least moderate RSV disease severity, where potentially greater treatment benefit can be achieved.
SYNOPSIS 3.1 Overview of Study Design 4.1 Inclusion Criteria	**Rationale:** The typographical error in the low dose for age group 1 was corrected from 0.83 to 0.85 mg JNJ-53718678/kg bodyweight.
SYNOPSIS 3.1 Overview of Study Design 6 DOSAGE AND ADMINISTRATION	**Rationale:** A clarification sentence was added regarding compliance with study drug administration.
TIME AND EVENTS SCHEDULE 7 STUDY DRUG COMPLIANCE 9.1.3 Double-Blind Treatment Phase	**Rationale:** The use of antitussives and mucolytics is recommended to be limited to use in line with the clinical practice guidelines and package inserts as they can potentially confound the evaluation of RSV signs and symptoms.
8 CONCOMITANT THERAPY 9.1.1 Overview 9.2.2 Clinical Course of RSV Infection	**Rationale:** Minor corrections and clarifications were made throughout the document.

Amendment 5 (10 July 2020)

The overall reason for the amendment: The overall reason for the amendment is to implement recommendations from Health Authorities (HA). Given that Cohort 1 enrollment has completed and no more Cohort 1 subjects are ongoing in the study, the changes listed below are only applicable for the newly to be recruited Cohort 2 subjects.

Applicable Section(s)	Description of Change(s)
	Rationale: A clarification was added to specify the timing of ECG monitoring on Day 3 to be performed at t_{max} of JNJ-53718678 at steady state (time to reach C_{max}), ie, approximately 1 hour post dose, in line with recommendations by HA
TIME AND EVENTS SCHEDULE 1.2.5 Overall Benefits/Risks	**Rationale:** The study intervention discontinuation and withdrawal criterion specific to ECG QT interval changes was adapted from values >500 ms to values ≥500 ms, in line with recommendations by HA.
9.3 Safety Evaluations 9.3.1 Specific Toxicities and Safety Topics of Special Interest 10.3 Discontinuation of Study Treatment	**Rationale:** The BCRP inhibitors eltrombopag and curcumin were added to the disallowed concomitant therapy section. JNJ-53718678 is a substrate for BCRP based on in vitro data. Clinically relevant BCRP inhibitors are prohibited to avoid potential DDI with JNJ-53718678, in line with recommendations by HA.
1.2.5 Overall Benefits/Risks 8 CONCOMITANT THERAPY	**Rationale:** Additional flexibility was provided with regards to the day of the C_{trough} sampling, as JNJ-53718678 trough concentrations are determined by the timepoint (at least 4 hours after the AM and before the PM dose) after dosing, and not by the day of sampling.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.4.1 Evaluations	**Rationale:** Removal of azithromycin as generally allowed medication. Azithromycin is a QT prolonging drug allowed with restrictions. Correction to an oversight of the previous amendment related to disallowed concomitant medications with QT-prolonging effects.
8 CONCOMITANT THERAPY	**Rationale:** Minor corrections and clarifications were made throughout the document.

Amendment 4 (26 May 2020)

The overall reason for the amendment: The overall reason for the amendment is to implement a risk mitigation plan following identification of an exposure (C_{max})-related important potential risk of QT interval prolongation identified in the TQT Study 53718678RSV1009 in healthy adult subjects. Given that Cohort 1 enrollment has completed and no more Cohort 1 subjects are ongoing in the study, the changes listed below are only applicable for the newly to be recruited Cohort 2 subjects.

Applicable Section(s)	Description of Change(s)
	Rationale: A new important potential risk of QT interval prolongation was identified from the above-mentioned TQT study and this was reflected in the benefit-risk section of the protocol.
1.1 Background 1.2.4 Potential Risks 1.2.5 Overall Benefits/Risks	
	Rationale: Recently available relevant clinical data were included in the introduction. Accordingly, the Investigator's Brochure Addendum to Edition 06 was added as a reference.
1 INTRODUCTION 1.1 Background 1.2.1 Known Benefits 1.2.2 Potential Benefits 1.2.4 Potential Risks 1.2.5 Overall Benefits/Risks	
	Rationale: The daily dosing frequency was changed from qd to bid dosing while maintaining the total daily dose (ie, at each intake half of the total daily dose will be administered). The proposed bid dosing will ensure mitigation of the important potential risk of QT interval prolongation and the highest potential antiviral effect while minimizing the risk of development of resistance. The definitions of missing dose and overdose were adapted accordingly. The generalized Multiple Comparison Procedure-Modeling approach in the statistical methods has been clarified regarding bid dosing.
SYNOPSIS TIME AND EVENTS SCHEDULE 1.2.5 Overall Benefits/Risks 1.3 Overall Rationale for the Study 3.1 Overview of Study Design 3.2 Study Design Rationale 6 DOSAGE AND ADMINISTRATION 7 STUDY DRUG COMPLIANCE 9.1.3 Double-Blind Treatment Phase 11.4.1.1 Primary Endpoint 11.4.1.2 Secondary Endpoints 11.4.2 Clinical Course of RSV Infection	
	Rationale: Changes in PK schedule are required to collect a PK sample at the C_{max} for each patient and a PK sample in the distribution/elimination phase. This allows the characterization of PK parameters for safety related to the risk of QT prolongation (C_{max}) and efficacy (AUC and C_{trough}) in all patients.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.4.1 Evaluations	
	Rationale: The frequency of ECG monitoring was increased by adding measurements at Day 1 (1 hour post dose) and Day 3 to enhance the cardiac-related safety follow-up.

Applicable Section(s)	Description of Change(s)
TIME AND EVENTS SCHEDULE 1.2.5 Overall Benefits/Risks	**Rationale:** Close monitoring of the use of concomitant medications to be conducted regularly was added as one of the QT prolongation mitigation measures to ensure the subjects' safety.
1.2.5 Overall Benefits/Risks	**Rationale:** Several exclusion criteria related to cardiac safety were added. Exclusion criterion 15 was made more stringent for children ≤3 years (ie, confirmed QTcF interval >450 ms) to ensure subjects' safety.
SYNOPSIS 1.2.5 Overall Benefits/Risks 4.2 Exclusion Criteria	**Rationale:** New physiologically based pharmacokinetics data indicate potential for increase of the JNJ-53718678 C_{max} due to CYP3A4 inhibition which in view of the QT interval prolongation risk needs to be avoided to maintain the safety margin. Therefore, moderate CYP3A4 inhibitors were added to the disallowed prescription medications 14 days prior to screening until 3 days after last dose (in addition to the already disallowed strong CYP3A4 inhibitors) to ensure no effect of the moderate and strong CYP3A4 inhibitors on the study intervention. Given that the $t_{1/2}$ of JNJ-53718678 is approximately 10 hours, study intervention is washed out after 3 days. Therefore, the period for strong CYP3A4 inhibitors being disallowed was aligned with that for moderate ones, ie, to 3 days after last study intervention intake.
1.2.5 Overall Benefits/Risks 8 CONCOMITANT THERAPY	**Rationale:** Medications with a known risk to prolong the QT interval cannot be initiated at screening and/or during the study intervention treatment period in view of the identified potential risk of QT interval prolongation.
1.2.5 Overall Benefits/Risks 8 CONCOMITANT THERAPY	**Rationale:** Specific toxicity management for cardiac events potentially related to QT prolongation was added to ensure the subjects' safety.
1.2.5 Overall Benefits/Risks 9.3.1 Specific Toxicities and Safety Topics of Special Interest	**Rationale:** A study intervention discontinuation and withdrawal criterion specific to QT interval changes to values >500 ms on ECG was added to ensure the subjects' safety.
1.2.5 Overall Benefits/Risks 10.3 Discontinuation of Study Treatment	**Rationale:** A safety measure regarding hypokalemia and hypomagnesemia was added.
TIME AND EVENTS SCHEDULE 1.2.5 Overall Benefits/Risks 9.3 Safety Evaluations	**Rationale:** The specific Rash Management section, which is a therapeutic area-specific section that can be adapted based on emerging data, has been removed as data from both adult and pediatric studies has not indicated rash-related safety signal.
9.3.1 Specific Toxicities and Safety Topics of Special Interest 10.3 Discontinuation of Study Treatment ATTACHMENTS	**Rationale:** A table presenting the risk factors for severe RSV disease was added to avoid stratification errors.

Applicable Section(s) Description of Change(s)
3.1 Overview of Study Design
Rationale: The statement on additional interim analyses (already included in the protocol body) was added to the synopsis and Section 3.1 for completeness.
SYNOPSIS 3.1 Overview of Study Design
Rationale: A statement was added on sharing selected unblinded data with investigators to support the revised risk-benefit evaluation for the current study and to support start of Phase 3.
SYNOPSIS 11.1 Interim Analyses
Rationale: A clarification was added (ULN are adult ULN) to the creatinine values of subjects older than 3 months of age in Attachment 1 (DMID Pediatric Toxicity Tables) based on feedback from the DMID Authors.
Attachment 1: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007; draft)
Rationale: The medication log was updated given the change in dose regiment from qd to bid. In order to make efficient updates to the ePRO system, the initial study medication log with slight modification will be repeated to allow capturing of dose intake information bid.
Attachment 6: Study Medication Log
Rationale: The Anticipated Event Review Committee was re-named to Safety Assessment Committee.
Attachment 3: Anticipated Events
Rationale: COVID-19-related measures were added to avoid co-infection with SARS-COV-2 as this would confound evaluation of the clinical course of RSV and to provide guidance on study conduct during the COVID-19 pandemic.
TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 4.1 Inclusion Criteria 4.2 Exclusion Criteria Attachment 10: Guidance on Study Conduct During the COVID-19 Pandemic
Rationale: An inconsistency was corrected from 50 to 55% with regards to the maximum % of subjects enrolled with time since onset of RSV symptoms of >3 days to ≤5 days at the time of all planned interim or final analyses.
3.2 Study Design Rationale
Rationale: Minor corrections and clarifications were made throughout the document.

Amendment 3 (20 December 2019)

The overall reason for the amendment: The overall reason for the amendment is to allow unblinding of the central sponsor team and selected local sponsor representatives from Japan to the data included in the second interim analysis and to allow unblinding of the sponsor, including the study team, and selected local sponsor representatives from Japan to all interim analyses planned after the second interim analysis.

Applicable Section(s)	Description of Change(s)
SYNOPSIS 11.1 Interim Analyses	**Rationale:** Based on the decision of the Sponsor Committee after the second interim analysis, the sponsor wants to proceed with further development and start the next JNJ-53718678 pediatric study(ies) in the Northern Hemisphere season of 2020/2021. Due to the non-confirmatory nature of Study 53718678RSV2002, and the aim to explore multiple potential clinical endpoints across 2 settings (hospital and community), the central sponsor team and selected local sponsor representatives from Japan will be unblinded to the data included in the second interim analysis upon recommendation from the IDMC and the Sponsor Committee to enable preparations for future study(ies) and to support associated health authority interactions. Any interim analysis planned after the second interim analysis will be unblinded to the sponsor, including the central study team, and selected local sponsor representatives from Japan to allow internal decision making and proceeding towards Phase 3. Investigators, subject(s), and local sponsor representatives (except selected local sponsor representatives from Japan) will remain blinded during and after all interim analyses. Medical writers were added to the central sponsor team.

Amendment 2 (5 July 2019)

The overall reason for the amendment: The overall reason for the amendment is to clarify how the required balance within the symptom onset randomization strata (symptom onset ≤3 days and >3 days to ≤5 days) for each of the interim analyses as well as for the final analysis will be achieved while allowing some flexibility in view of RSV seasonality and reducing the recruitment impact of a (temporary) pause in enrollment in one of the strata.

Applicable Section(s)	Description of Change(s)
	Rationale: Clarifications are provided on how the required balance within the symptom onset randomization strata (symptom onset ≤3 days and >3 days to ≤5 days) for each of the interim analyses as well as for the final analysis will be achieved while allowing some flexibility in view of RSV seasonality and reducing the recruitment impact of a (temporary) pause in enrollment in one of the strata. Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects can be enrolled in the >3 days to ≤5 days stratum). Enrollment in the >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. Stratum caps and closures are managed separately for each cohort and consider the sample size of the respective cohort for the interim analysis and the total sample size of each cohort for the final analysis. Prior to interim analysis 2 (at N=approximately 70-80 in Cohort 1), the temporary pause will occur once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Prior to interim analysis 3 (at N=approximately 70-80 in Cohort 2) and prior to interim analysis 4 (at N=approximately 150 in the Cohort 2), the temporary pause will occur once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for the corresponding interim analysis has been randomized. For the final analysis, enrollment in the >3 days to ≤5 days since symptom onset stratum will be stopped once the maximum number of subjects are enrolled in this stratum in both cohorts. Since the number of subjects enrolled in Cohort 2 is the trigger to perform interim analysis 3 and interim analysis 4, enrollment in Cohort 1 in the >3 days to ≤5 days since symptom onset stratum might be stopped, at any time after interim analysis 2, once the maximum number of subjects in this stratum are enrolled for the final analysis.

Applicable Section(s)	Description of Change(s)
SYNOPSIS 3.1 Overview of Study Design 3.2 Study Design Rationale 4.1 Inclusion Criteria 5 TREATMENT ALLOCATION AND BLINDING 11.1 Interim Analyses 11.12 Independent Data Monitoring Committee	**Rationale:** Clarification that the clinical course endpoints will be evaluated in Cohort 1 and Cohort 2 separately, and will be compared between the 2 cohorts, because of potential differences between the 2 cohorts.
11.3.2 Key Secondary Objective: Clinical Course Effect 11.4.2 Clinical Course of RSV Infection	**Rationale:** Clarification that clinical evaluation does not have to be repeated in case Cohort 2 Screening and Randomization occur on the same calendar day, because it is a once daily procedure in the outpatient setting.
TIME AND EVENTS SCHEDULE	**Rationale:** The PRESORS version 7.1 that was replaced incorrectly by version 7.2 in protocol Amendment 1, was reversed to PRESORS version 7.1 from the original protocol.
Attachment 6: Parent(s)/Caregiver(s) PRESORS v7.1 (9 July 2018)	**Rationale:** Minor clarifications were made throughout the protocol.
Throughout the protocol	

Amendment 1 (14 May 2019)

The overall reason for the amendment: The overall reason for the amendment is to increase the sample size of Cohort 1 (hospitalized cohort) from 24 to 48 subjects per treatment arm to increase the precision on the estimates for the clinical course related endpoints in this cohort.

Applicable Section(s)	Description of Change(s)
SYNOPSIS 11.3 Sample Size Determination	**Rationale:** The sample size of Cohort 1 was increased from 24 to 48 subjects per treatment arm (approximately 144 subjects in total in this cohort) to increase the precision on the estimates for the clinical course related endpoints in this cohort. Assuming a median time to resolution of symptoms of 3 days in the placebo group, a 1-day reduction in the active group (ie, ratio of active versus placebo of 66%), and a scale parameter of 1/0.65, a sample size of 48 subjects will attain 95% probability to reach an observed effect in the right direction; based on estimates derived from an accelerated failure time model.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 4 SUBJECT POPULATION 4.1 Inclusion Criteria 9.1.2 Screening Phase 9.1.3 Double-Blind Treatment Phase	**Rationale:** It was clarified that randomization should occur within 48 hours after the collection of the standard of care (SOC) sample used for RSV diagnosis (instead of having results available), to better standardize the (pre)screening window.

Applicable Section(s)	Description of Change(s)
	Rationale: Addition of heel prick for PK-related blood collection to allow sites to use either method as per their SOC.
SYNOPSIS TIME AND EVENTS SCHEDULE 1.2.4 Potential Risks 9.4.1 Evaluations	
	Rationale: An error in Figure 1 was corrected.
3.1 Overview of Study Design	
	Rationale: Addition of statement to disallow subjects whose mother received an investigational RSV vaccination during the pregnancy for this child and whose age is <3 months at time of screening, to eliminate any confounding of the presence of maternal antibodies on the clinical course and antiviral effect.
SYNOPSIS 4.2 Exclusion Criteria 8 CONCOMITANT THERAPY	
	Rationale: The wording of 'total blood volume to be collected' was changed into a maximum regardless of bodyweight. The total blood volume is in line with the WHO guidance for allowable pediatric blood volume in clinical research.
9.1 Study Procedures 16.1 Study-Specific Design Considerations	
	Rationale: Removal of fax-based serious adverse events reporting because of its replacement by a new electronical reporting system per company process change.
12.3.2 Serious Adverse Events	
	Rationale: The protocol was updated to indicate that if a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL each). This will lessen the burden for subjects by limiting the required number of mid-turbinate nasal swabs.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.1.2 Screening Phase 9.3 Safety Evaluations	
	Rationale: It was clarified that the subject's diagnosis of RSV infection at screening should be performed using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred), or a rapid antigen detection assay. This wording for other molecular-based assay was added to use the more general classification of molecular-based assays, which includes PCR. In addition, it was clarified that a rapid assay is preferred to allow fast RSV diagnosis to minimize the screening duration.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 4.1 Inclusion Criteria 9.1.2 Screening Phase	

Applicable Section(s)	Description of Change(s)
	Rationale: The protocol was updated to remove potential for drug-drug-interaction (DDI) as safety topic of special interest based on the evaluation of newly available nonclinical and clinical data. These data mainly indicate an increase in JNJ-53718678 exposure when co-administered with strong CYP3A4 inhibitors. Given safety measures are in place to ensure the subject's safety in this clinical study and because strong CYP3A4 inhibitors are not allowed as per Section 8, the sponsor no longer considers the potential for DDI a safety topic of special interest.
1.2.4 Potential Risks	
	Rationale: The protocol was updated to remove effects on blood coagulation as safety topic of special interest based on the evaluation of all available data, including most recent nonclinical and clinical data. Based on this evaluation, no signal with respect to blood coagulation has been observed to date, and hence the sponsor no longer considers effects on blood coagulation a safety topic of special interest. In line with this decision, coagulation testing (which requires an additional blood draw) was removed from the Time and Events Schedule. Consequently, the maximum total blood volume collected decreases.
TIME AND EVENTS SCHEDULE 1.2.4 Potential Risks 9.1.2 Screening Phase 9.3 Safety Evaluations 9.3.1 Specific Toxicities and Safety Topics of Special Interest	
	Rationale: The protocol was updated to clarify that responses to some of the identifying questions for parent(s)/caregiver(s) in the eDiary are optional in order to comply with the European regulation on general data protection.
Attachment 6:	Parent(s)/Caregiver(s) PRESORS v7.1 (9 July 2018)
	Rationale: The protocol was updated to remove any reference to the long-term observational follow-up as this study is no longer planned as per sponsor's decision.
SYNOPSIS 3.1 Overview of Study Design	
	Rationale: The Time and Events Schedule was updated to add the monitoring of the completion of the parent(s)/caregiver(s) Pediatric RSV Electronic Severity and Outcome Rating Scales (PRESORS) by the site staff to align with the body of the protocol and for clarification.
TIME AND EVENTS SCHEDULE	
	Rationale: Minor grammatical, formatting, or spelling changes were made throughout the protocol because minor errors were noted.
Throughout the protocol and in Attachment 1	

SYNOPSIS

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

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.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

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.

Secondary Objectives

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 pharmacokinetics (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 pharmacodynamics (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

Exploratory Objectives

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)

Endpoints

Primary Endpoint

The primary efficacy endpoint is the RSV viral load area under the curve (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

The secondary endpoints are:

- 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 (ie, 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)

- respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) over time as measured by the investigator during scheduled visits.
- body temperature as measured by parent(s)/caregiver(s) and recorded in the temperature log (for Cohort 1 after discharge and Cohort 2)
- need for (re)hospitalization during treatment and follow-up

in hospitalized subjects only:

- 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 (ie, without requirement of supplemental oxygen compared with pre-RSV infection status)
- time to discharge (from initial admission and from initiation of treatment)
- time to clinical stability, with clinical stability evaluated by the investigator (from initial admission and from initiation of treatment)
- 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 (eg, not transferred to ICU due to bed availability)
  - requiring ICU level of care is defined by some specific conditions:
    - acute or imminent respiratory failure
    - treatment of complicated acid-base or electrolyte imbalances
    - cardiogenic shock
    - acute congestive heart failure
    - hemodynamic instability
  - having other conditions requiring specialized equipment and/or staff competencies only available in the ICU
- need for and duration of supplemental oxygen (regardless of method used); 'need for supplemental oxygen' is defined by:
  - requiring invasive mechanical ventilation
  - requiring 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 noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation)
- o need for hydration and/or feeding by intravenous (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

Exploratory endpoints include:

- the occurrence of complications with onset after treatment initiation that are associated with RSV per investigator assessment:

  bacterial superinfections (eg, pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment)

  otitis media, bronchiolitis, viral pneumonia

exacerbations of underlying pulmonary disease (eg, 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 (eg, nasopharyngeal and/or tracheal aspirate samples)
- virologic parameters derived from the RSV viral load as measured by quantitative viral culture

Hypothesis

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV (ie, a decrease in RSV viral load 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.

OVERVIEW OF STUDY 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 [Cohort2]).

Subjects with at least mild RSV disease will be enrolled (ie, at least one symptom of upper respiratory tract infection, at least one symptom of lower respiratory tract infection, and at least one systemic/general symptom). Eligible subjects can be otherwise healthy or have a risk factor for severe RSV disease (eg, prematurity at birth [only for subjects ≥3 months of age at the time of consent] or having a comorbid condition eg, bronchopulmonary dysplasia, congenital heart disease, other congenital diseases, Down syndrome, neuromuscular impairment, cystic fibrosis, or recurrent wheezing/asthma). Subjects who are immunocompromised are excluded.

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 interim analysis (see below).

Study participants will be identified when they are hospitalized or expected to be hospitalized within 24 hours after presentation to the hospital (Cohort 1) or present for medical care as outpatients (Cohort 2) with symptoms of an acute respiratory illness supporting a diagnosis of RSV infection (eg, nasal congestion, rhinorrhea, pharyngitis, increased respiratory effort, abnormal breathing sounds [wheezing, rales, or rhonchi], cyanosis, cough, apnea, fever, feeding difficulties, dehydration). For newly enrolled subjects in Cohort 2 after Protocol Amendment 6, cough or wheezing should be accompanied by at least one additional lower respiratory tract infection (LRTI) sign/symptom in order to be eligible. 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.

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).

Screening must be completed as soon as possible. During screening, a study-specific screening sample (mid-turbinate swab) will be collected for the local diagnosis of RSV infection using a (preferably) rapid PCR- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main informed consent form [ICF] or with the diagnostic study ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.

A (separate) mid-turbinate swab will be collected immediately prior to the first dose for central laboratory analyses to confirm RSV infection (and subtype), to determine the RSV viral load, to perform viral sequencing, and to determine the presence of other viral or bacterial pathogens. If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL).

Initially, only hospitalized subjects will be recruited (Cohort 1). 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 (see below).

Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis (in case swabs collected per local SOC testing were used for the local diagnosis of RSV infection), whichever comes first. 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). 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 as defined above). Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects can be enrolled in the >3 days to ≤5 days stratum). To guarantee the required balance between strata for the interim analyses, enrollment in the >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. Stratum caps and closures are managed separately for each cohort and consider the sample size of the respective cohort for the interim analysis and the total sample size of each cohort for the final analysis.

Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. JNJ-53718678/placebo can be administered with/without food. The study drug will be administered orally using a dosing syringe. For Cohort 1 and during hospitalization, the study drug can also be administered through a nasogastric tube, if already in place. In this document, both administration methods are referred to as “oral dosing”, unless specified otherwise.

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 interactive web response system [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).

Study drug will be administered twice daily for 7 days (14 consecutive doses). Doses are based on weight and age group:

- High Dose (Cohort 1: n = 48 [target]; 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 1: n = 48 [target]; 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 1: n = 48 [target]; Cohort 2: n = 50 [target]): those randomized to a placebo regimen will be subsequently 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)

Note: The above-mentioned doses refer to the amount of JNJ-53718678-AAA (free form). 20 mg JNJ-53718678-AAA corresponds to 23 of mg JNJ-53718678-ZCL (hemi-tartrate salt of JNJ-53718678-AAA) used in the oral suspension.

In Cohort 1, the study drug will be administered by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel during hospitalization. In case the subject is discharged prior to Day 7, the study drug will continue to be administered at home by the parent(s)/caregiver(s) through Day 7. In Cohort 2, the first dose of study drug will be administered, by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel, at the study site; the study drug will continue to be administered at home by the parent(s)/caregiver(s) through Day 7 or the morning (AM) of Day 8 if the first dose was given PM on Day 1. All subjects will receive standard supportive care for RSV infection as per local SOC considering pre-defined restrictions. All SOC treatment should be recorded as concomitant medication/treatment.

In Cohort 1, subjects can be discharged as of Day 2 if deemed appropriate by the investigator and after completion of the required investigator-performed assessments for that day (except for the evening assessment in case the assessment is to be performed twice daily [bid]). Discharged subjects (Cohort 1) will be required to attend the scheduled study visits as outpatients with the same visit schedule as Cohort 2 subjects, from time of discharge onward. Cohort 2 subjects will have study visits on Day 3, Day 5, Day 8, Day 14, and on Day 21. All scheduled study visits can also be done as home visits, if feasible for the study

site and if allowed per local regulations. On Day 28 (±3), subject's parent(s)/caregiver(s) will be contacted by the site staff for a telephone follow up visit, after which the subject completes the study. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 Follow-Up Visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit for the subject at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28.

In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

As an evaluation of antiviral activity, the RSV viral load in nasal secretions will be measured at the central lab using a qRT-PCR assay on mid-turbinate nasal swab specimens, which will be collected at several timepoints during the study. If feasible, the RSV infectious virus load may also be assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples.

Viral resistance will be monitored by sequencing of the F-gene in all baseline samples, and on subsequent samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at discretion of the sponsor's virologist. Sequencing data will not be reported to the investigators. Sequencing results may be presented in a separate report.

Clinical course and severity of RSV infection will be assessed through different measures.

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and physical examination will be assessed throughout the study from signing of the ICF until the subject's last study-related activity.

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model. 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 (see table with overview of PK sampling window below [section Pharmacokinetic Evaluations]). 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 at this site. For the subjects recruited to Cohort 2 after Protocol Amendment 4, PK samples will be collected approximately one hour after administration of study drug (after the ECGs are obtained if applicable) at Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

Medical resource utilization and acceptability and palatability of the study drug will be assessed.

Leftover mid-turbinate nasal swab and blood samples collected for other testing may be used for exploratory biomarker analyses to determine the effects of JNJ-53718678 on markers of RSV disease, at discretion of the sponsor.

An IDMC will be commissioned for this study and will review unblinded safety data on a regular basis 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 to the Sponsor Committee to ensure the safety of enrolled subjects. The IDMC can recommend to the Sponsor Committee to halt a dose arm due to safety concerns. The IDMC will also review the data of the interim analyses and provide recommendations

to the Sponsor Committee. The Sponsor Committee will take a decision considering the IDMC's recommendation.

The study will start with Cohort 1 (including the subcohort). The first interim analysis encompassing safety and tolerability, PK, and antiviral effect is planned when at least 36 subjects from Cohort 1 have completed the Day 14 assessments (or discontinued earlier). Enrollment in Cohort 1 will continue during the 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 (see below).

A second interim analysis is planned, 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) have completed the Day 14 assessments (or discontinued earlier). During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity and one clinical endpoint (ie, time to resolution of symptoms, considering data of both cohorts), 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, other clinical course and safety-related endpoints, will be analyzed. The Sponsor Committee will take a decision considering the IDMC's recommendation. Depending on enrollment status of Cohort 2, the second interim analysis will not be performed, if it is later than or too close to the predicted timing of the planned third interim analysis.

A third interim analysis is planned, preferably at the end of a hemispheric RSV season, when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier) and will include all available data from Cohort 1 and Cohort 2. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity (data from both cohorts combined) and clinical endpoints (Cohort 2 data only), as well as a sample-size re-estimation for clinical endpoints (Cohort 2 data only). Both the study team and the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account. The maximum number of subjects in Cohort 2 in the study will not exceed 300.

If the study is extended beyond the initially planned sample size in Cohort 2 for the primary analysis (N=150), a fourth interim analysis will be performed preferably at the end of a hemispheric RSV season, after approximately 150 subjects in Cohort 2 have completed the Day 14 assessments (or discontinued earlier), and will include all available data from Cohort 1 and Cohort 2. The primary analysis on antiviral activity will be performed during this fourth interim analysis 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 preparations, including regulatory interactions. In addition, the futility and population enrichment analysis will be repeated at this interim analysis. Both the study team and the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account.

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 will coincide with the primary analysis. Additional interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities.

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.

During and after all interim analyses, investigators, subject(s), and local sponsor representatives (except for selected local sponsor representatives from Japan) will remain blinded. An IDMC will monitor and review data in an unblinded manner, at all interim analyses. During the first interim analysis, the Sponsor Committee will be unblinded; the central sponsor team members and local sponsor representatives from Japan will remain blinded. For the second interim analysis, the Sponsor Committee, central sponsor team members, and selected local sponsor representatives from Japan will be unblinded upon recommendation from the IDMC and the Sponsor Committee. During any interim analysis taking place after the second interim analysis, the sponsor, including the central study team, and selected local sponsor representatives from Japan will be unblinded. Aggregate unblinded data and certain individual safety events may be shared with investigators to support the revised risk-benefit evaluation for the current study and to support start of Phase 3.

A separate substudy may be performed at selected study sites to explore the feasibility of the use of biosensors for the evaluation of cardio-respiratory parameters (eg, respiratory rate, heart rate, and SpO_2). Details, including objectives and study design, will be described in a separate substudy protocol.

SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible after initial presentation at the hospital (Cohort 1) or after presentation for medical care as outpatients (Cohort 2) such that subjects are randomized within 5 days of symptom onset. 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 as defined above).

Key Inclusion Criteria

- The subject is a boy or girl ≥28 days and ≤3 years at the time of consent.
- The subject has been diagnosed with RSV infection using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay.

  Note: If a subject had a positive similar RSV diagnostic test from another study for which (s)he was otherwise ineligible or a SOC test within 24 hours prior to start of screening and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first.

  Note: If a rapid antigen detection assay is used as part of SOC or study-specifically (with the main study ICF or with the diagnostic ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.
- The subject has an acute respiratory illness with at least 1 of the signs/symptoms listed in each of the following categories within 24 hours prior to start of screening and at screening, as evaluated by the investigator:

  Upper respiratory tract infection: nasal congestion, rhinorrhea, pharyngitis, or otitis media; AND

  LRTI: increased respiratory effort (as evidenced by subcostal, intercostal or tracheosternal retractions, grunting, head bobbing, nasal flaring or tachypnea), abnormal breathing sounds

(wheezing, rales or rhonchi), cyanosis, apnea, or cough (cough or wheezing should be accompanied by at least one additional LRTI sign/symptom in order to be eligible); AND

Systemic/general: feeding difficulties, defined as <75% intake of normal food amounts; dehydration; fever; disturbed sleep or disturbed activity level (irritable/restless/agitated/less responsive)

- The time of onset of RSV symptoms to the anticipated time of randomization must be ≤5 days. Onset of symptoms is defined as the time of the day (or part of the day if time of the day cannot be specified) the parent(s)/caregiver(s) became(s) aware of the first sign and/or symptom consistent with respiratory or systemic/general manifestation of symptoms of RSV infection. The time of symptom onset has to be assessed as accurately as possible.

  Note: Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects could be enrolled in the >3 days to ≤5 days stratum).

- Except for the RSV-related illness, the subject must be medically stable based on physical examination, medical history, and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying condition (RSV disease and/or present risk factor[s] for severe RSV disease) in the study population as evaluated by the investigator. This determination must be recorded in the subject's source documents and initialed by the investigator.

Key Exclusion Criteria

- The subject is <3 months postnatal age at screening and was born prematurely (ie, <37 weeks and 0 days of gestation).
- The subject has major congenital anomalies or known cytogenetic or metabolic disorders other than the ones allowed above. ***Note***: Isolated open ductus arteriosus and open foramen ovale are not exclusionary as these are not considered major anomalies. Subjects with congenital heart disease, cystic fibrosis, congenital diaphragmatic hernia, or Down Syndrome are allowed to participate.
- The subject is considered by the investigator to be immunocompromised within the past 12 months, whether due to underlying medical condition (eg, malignancy or genetic disorder other than immunoglobulin A deficiency, or known human immunodeficiency virus [HIV] infection) or medical therapy (eg, immunomodulators other than corticosteroids for the treatment of comorbidities, chemotherapy, radiation, stem cell or solid organ transplant).
- The subject is being treated with extracorporeal membrane oxygenation (Cohort 1 only).
- The subject is receiving chronic home oxygen therapy at screening.
- The subject has other clinically significant abnormal ECG findings not consistent with the present risk factor for severe RSV disease (if applicable) in the study population, as judged by the investigator based on the machine read ECG results at screening.
- The subject has a QT interval corrected for heart rate according to Fridericia's formula (QTcF) interval >450 ms per the machine read (mean of triplicate) parameter result confirmed by repeat ECG recording during screening.
- The subject's mother received an investigational RSV vaccination during the pregnancy for this child whose age is <3 months at time of screening.
- The subject has evidence of one of the following ECG abnormalities per the machine read ECG result confirmed by repeat ECG recording at screening:

  Repetitive premature ventricular contractions (>10/min)

Second- or third-degree heart block

Complete or incomplete left bundle branch block or complete right bundle branch block

- The subject has a personal or first- or second-degree family history of long QT syndrome or sudden cardiac death.

DOSAGE AND ADMINISTRATION

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. Subjects randomized to a placebo regimen are subsequently randomized in a 1:1 ratio to receive placebo matching either the volume of the high or of the low dose. Doses are based on weight and age group (3 age groups [≥28 days and <3 months; ≥3 months and <6 months, or ≥6 months and ≤3 years of age] are defined depending on the subject's age at the time of consent). An overview of the treatments for Cohort 2 newly recruited subjects is provided in the table below.

Treatment		Age Group[a]	Dosing Regimen[b,d]	Volume
High dose		1	2.5 mg/kg bid on Days 1 to 7	A mL[c] oral suspension of JNJ-53718678
		2	3.0 mg/kg bid on Days 1 to 7	C mL[c] oral suspension of JNJ-53718678
		3	4.5 mg/kg bid on Days 1 to 7	E mL[c] oral suspension of JNJ-53718678
Low dose		1	0.85 mg/kg bid on Days 1 to 7	B mL[c] oral suspension of JNJ-53718678
		2	1.0 mg/kg bid on Days 1 to 7	D mL[c] oral suspension of JNJ-53718678
		3	1.5 mg/kg bid on Days 1 to 7	F mL[c] oral suspension of JNJ-53718678
Placebo	Match high dose	1,2, or 3	placebo bid on Days 1 to 7	A, C, or E (respectively) mL[b] placebo
	Match low dose	1,2, or 3	placebo bid on Days 1 to 7	B, D, or F (respectively) mL[b] placebo

a. Age Group 1: ≥28 days and <3 months; Age Group 2: ≥3 and <6 months; Age Group 3: ≥6 months and ≤3 years.
b. Doses are provided for JNJ-53718678-AAA.
c. A to F represents the volume of oral JNJ-53718678 suspension to obtain the required dose of JNJ-53718678-AAA or the volume of the matching placebo suspension. JNJ-53718678 is formulated as an oral suspension containing 23 mg/mL microfine JNJ-53718678-ZCL, the hemi-tartrate salt of JNJ-53718678-AAA, which is equivalent to 20 mg/mL JNJ-53718678-AAA, to be used depending on the bodyweight of the subject (and the required volume to be administered). The required volume to be administered per intake will be calculated by the IWRS and provided to the sites.
d. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total.

Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1.

Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. The study drug can be administered with/without food. The study drug will be administered orally using a dosing syringe. For Cohort 1 and during hospitalization, the drug can also be administered through a nasogastric tube, if already in place.

Note: Prior to Protocol Amendment 4, the total daily dose was the same but the daily dosing frequency was qd instead of bid.

- Cohort 1:

  During hospitalization: the study drug will be administered by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel. Date and time of dosing will be recorded by the site staff.

  After Discharge: parent(s)/caregiver(s) will administer study drug at home if the subject is discharged prior to Day 7. Date and time of dosing will be captured in the study medication log, to be completed by the parent(s)/caregiver(s) in the provided electronic device.

- Cohort 2, the first dose of study drug will be administered, by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel, at the study site. On Day 1, date and time of dosing will be recorded by the site staff. At home, date and time of dosing will be captured in the study medication log, to be completed by the parent(s)/caregiver(s) in the provided electronic device.

Study site personnel will instruct subjects' parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing as per sponsor provided investigational product preparation instruction (IPPI).

EFFICACY EVALUATIONS

Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal mid-turbinate swab samples will be measured at the central lab using a qRT-PCR assay. Mid-turbinate swab specimens for the determination of RSV viral load will be collected at several timepoints during the study. Date and time of sampling will be collected. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). The nostril that was sampled will be documented by the site staff (nasal swabs taken on-site) or by parent(s)/caregiver(s) (nasal swabs taken at home).

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

RSV RNA viral load can also be 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 SOC, which may be used to assess virologic parameters.

The RSV infectious virus load as measured by quantitative culture of RSV (plaque assay), if feasible, on selected nasal swab samples, may be used to assess virologic parameters.

Clinical Severity and Clinical Course of RSV Infection

The study will include the following evaluations of the clinical course of RSV infection:

- Cohort 1 and Cohort 2:

  clinical parameters: respiratory rate, heart rate, SpO_2 and body temperature 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 (refer to the substudy Clinical Protocol for detailed information).

  body temperature as measured by parent(s)/caregiver(s) and recorded in the temperature log (for Cohort 1 after discharge and Cohort 2)

  evolution and severity of signs and symptoms of RSV disease (fever, cough, sputum, wheezing, difficulty breathing, nasal congestion, feeding issues) as assessed by the parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) and the clinician (clinician PRESORS)

the need for (re)hospitalization

the occurrence of complications, bronchiolitis or viral pneumonia with onset after treatment initiation that are associated with RSV per investigator assessment

the need for antibiotics related to complications associated with RSV per Investigator assessment

- Cohort 1 only:

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

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

  level of and duration by level of hospital care (eg, ICU, transitional care unit, ward floor)

  oxygen requirement type (eg, supplemental oxygen, noninvasive pressure ventilation, endotracheal-mechanical ventilation), and duration

  hydration and feeding by IV line/nasogastric tube and duration

Viral Sequencing

Sequencing data will not be reported to the investigators. Viral resistance will be monitored by sequencing of the F-gene of the viral genome in all baseline nasal swab samples and in subsequent samples upon request of the sponsor's virologist. Other regions of the RSV genome may also be sequenced at discretion of the sponsor's virologist. The impact of the viral subtype and baseline genotype on the antiviral response will be explored. Sequencing results may be presented in a separate report.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity (end of study/early withdrawal).

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the electronic case report form (eCRF).

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

The study will include the following evaluations of safety and tolerability:

- Adverse Events
- Clinical Laboratory Tests
- Electrocardiogram (ECG)
- Vital Signs
- Physical Examination

PHARMACOKINETIC EVALUATIONS

Blood samples for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick at predefined timepoints. 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 (see Table below). 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 (see Table below). 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 at this site.

Table: Overview of Pharmacokinetic Sampling Windows for Cohort 1 Subjects

Pharmacokinetic Sampling Group	Visit Day 1	Visit Day 2	
	Time after dose intake at Visit 1	Time before dose intake at Visit 2	Time after dose intake at Visit 2
X	2 h – 5 h	-	30 min – 3 h
Y	5 h – 9 h	3 h – 1 min	-

For the subjects recruited to Cohort 2 after Protocol Amendment 4, PK samples will be collected approximately one hour after administration of study drug (after the ECGs are obtained if applicable) at Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

Samples may also be used for the analysis of metabolites of JNJ-53718678 or endogenous markers for enzymes or transporters involved in the metabolism and distribution of JNJ-53718678, at the discretion of the sponsor. Blood samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. The subject's confidentiality will be maintained.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Obtained PK and PD data (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be used to explore the relationship between the PK and PD parameters.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Assessments performed as part of the clinical course of RSV infection-related assessments

  Duration of hospitalization (total days length of stay, including duration by wards level [eg, ICU]) (Cohort 1 only).

  The number of subjects (proportion) who started antibiotic use after the first dose of study drug through the last study visit.

  Requirement for, and duration of, hospital (re)admission for respiratory reasons through the last study visit.

- Additional assessments

  Number and duration of medical care encounters and treatments (including physician or emergency room visits, tests and procedures, and medications, surgeries and other selected procedures; inpatient and outpatient).

ACCEPTABILITY AND PALATABILITY

Acceptability and palatability of the JNJ-53718678 formulation will be assessed through a questionnaire completed by parent(s)/caregiver(s) in the electronic device after last dosing.

BIOMARKERS

Leftover mid-turbinate nasal swab and blood samples collected for other testing may be used for exploratory biomarker analyses (eg, proteins including cytokines, microbiome), on the premise that these markers may play a role in the treatment response, safety of JNJ-53718678, or RSV-related disease.

Analyses of biomarkers may be performed at the sponsor's discretion and reported separately from this study.

No human deoxyribonucleic acid (DNA) analyses will be performed on these samples.

OTHER EVALUATIONS

Mid-turbinate nasal swabs collected immediately prior to first dosing will be used to determine the presence of viral (other than RSV) or bacterial pathogens (both by multiplex PCR) at the central laboratory.

STATISTICAL METHODS

Analyses will be performed on the combined dataset of hospital and outpatient subjects, as well as on data of each cohort separately.

Enrollment will continue during each of the interim analyses.

First Interim Analysis

The first interim analysis encompassing safety and tolerability, PK, and antiviral effect is planned when at least 36 subjects from Cohort 1 have completed the Day 14 assessments (or discontinued earlier). Enrollment in Cohort 1 will continue during the interim analysis and IDMC review.

Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 1 (at N=36 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 1 has been randomized.

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.

Second Interim Analysis

A second interim analysis is planned, 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) have completed the Day 14 assessments (or discontinued earlier). Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 2 (at N=approximately 70-80 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 2 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity and one clinical endpoint (ie, time to resolution of symptoms, considering data of both cohorts) 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, other clinical course and safety-related endpoints will be analyzed. The Sponsor Committee will take a decision considering the IDMC's recommendation. Depending on enrollment status of Cohort 2, the second interim analysis will not be performed, if it is later than or too close to the predicted timing of the planned third interim analysis.

Third Interim Analysis

A third interim analysis is planned, preferably at the end of a hemispheric RSV season, when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier) and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 3 (at N=approximately 70-80 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 3 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity (data from both cohorts combined) and clinical endpoints (Cohort 2 data only). The rules implement simultaneously a conditional success probability approach (viral load) and a Go-NoGo approach on multiple clinical endpoints. Both the study team and the IDMC will review the results of the interim analysis, and may recommend to the Sponsor Committee an early termination of the study for futility or to enrich the population and limit further enrollment to patients with ≤3 days since symptom onset, in case the conditional power on the viral load endpoint is regarded as being too low and/or the success probability of the clinical endpoints is too low. The Sponsor Committee will take a decision considering the recommendations from the study team and IDMC. The exact criteria of these non-binding decision rules will be defined in the statistical analysis plan (SAP).

No clinical endpoints for Phase 3 have been identified yet and the association between the antiviral effect and clinical course endpoints is not yet established for RSV. A key secondary objective of this Phase 2 study is the evaluation of clinical course endpoints and their dependence on viral load reductions. Results of this Phase 2 study will inform on discussion and selection of clinical course endpoints and guide the design for subsequent Phase 3 studies. Therefore, a sample size re-estimation based on clinical course endpoints (Cohort 2 data only) will be performed during interim analysis 3 and may result in an expansion of Cohort 2. Based on all available data from Cohort 2 at the cut-off for interim analysis 3, one or more clinically relevant and sensitive endpoint(s) will be selected for confirmation. Time to resolution (ie, 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 interim analysis 3 for the endpoint selection and sample size recalculation.

After selection of (a) clinical endpoint(s), the number of subjects in Cohort 2 will be calculated to minimize the conditional “consider”-probability for clinical endpoints (Go-NoGo-approach) at the end of the study assuming a required confidence of 90% (one-sided) to exclude the target value and/or the minimal acceptable value. Both the study team and the IDMC may recommend to the Sponsor Committee an increase of the sample size for Cohort 2 of the study. The maximum number of subjects in Cohort 2 in the study will not exceed 300.

Fourth Interim Analysis

If the study is extended beyond the initially planned sample size in Cohort 2 for the primary analysis (N=150), a fourth interim analysis will be performed preferably at the end of a hemispheric RSV season, after approximately 150 subjects in Cohort 2 have completed the Day 14 assessments (or discontinued earlier), and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 4 (at N=approximately 150 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 4 has been randomized. The primary analysis on antiviral activity will be performed during this fourth interim analysis 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 preparations, including regulatory interactions. In addition, the futility and population

enrichment analysis will be repeated at this interim analysis. Both the study team and the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account.

Final Analysis

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 will coincide with the primary analysis. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be stopped once the maximum number of subjects are enrolled in this stratum in both cohorts. Since the number of subjects enrolled in Cohort 2 is the trigger to perform interim analysis 3 and interim analysis 4, enrollment in Cohort 1 in the >3 days to ≤5 days since symptom onset stratum might be stopped, at any time after interim analysis 2, once the maximum number of subjects in this stratum are enrolled for the final analysis.

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.

To account for multiplicity, and to be able to define a robust clinical course endpoint for Phase 3, both unadjusted and adjusted p-values, with appropriate Type I error control, will be presented in the final analysis.

Additional interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities.

During and after all interim analyses, investigators, subject(s), and local sponsor representatives (except for selected local sponsor representatives from Japan) will remain blinded. An IDMC will monitor and review data in an unblinded manner, at all interim analyses. During the first interim analysis, the Sponsor Committee will be unblinded; the central sponsor team members and local sponsor representatives from Japan will remain blinded. For the second interim analysis, the Sponsor Committee, central sponsor team members, and selected local sponsor representatives from Japan will be unblinded upon recommendation from the IDMC and the Sponsor Committee. During any interim analysis taking place after the second interim analysis, the sponsor, including the central study team, and selected local sponsor representatives from Japan will be unblinded. Aggregate unblinded data and certain individual safety events may be shared with investigators to support the revised risk-benefit evaluation for the current study and to support start of Phase 3.

Sample Size

The basis of the sample size calculation is the antiviral results 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 the table below. Based on Study 53718678RSV1005 results, no discrimination between the proposed doses is expected (ie, E_{max} dose-response shape was observed).

Table 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 (eg, 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≥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 (ie, 20%).

In conclusion, 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).

During interim analysis 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 interim analysis, one or more clinically relevant and sensitive endpoint(s) will be selected for confirmation in the final analysis. Time to resolution (ie, 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 interim analysis 3 for the endpoint selection and sample size recalculation.

After selection of (a) clinical endpoint(s), the number of subjects in Cohort 2 will be calculated that is required to minimize the conditional “consider”-probability for clinical endpoints (Go-NoGo-approach) at the end of the study, assuming a required confidence of 90% (1-sided) to exclude the target value and/or the minimal acceptable value.

Both the study team and the IDMC may recommend to the Sponsor Committee an increase of the sample size for Cohort 2 of the study. The maximum number of subjects in Cohort 2 in the study will not exceed 300.

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 (ie, ratio of 66%), and a scale parameter of 1/0.65, a sample size of 48 subjects per treatment arm will reach 95% probability to reach an observed effect in the right direction; based on estimates derived from an accelerated failure time model. This will allow the evaluation of clinical course endpoints in the hospital population compared to the outpatients.

Efficacy Analyses

The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized subjects who received at least one dose of study treatment and who have a centrally confirmed RSV viral load of ≥1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) at baseline.

Primary Endpoint

The primary objective is to establish antiviral activity of JNJ-53718678. The primary efficacy endpoint is the RSV viral load area under the curve (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. 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.

A set of 3 candidate models will be used to cover a suitable range of possible dose-response shapes (linear, E_{max}, exponential). Doses of the different age groups will be pooled and transformed to the total daily dose of the oldest age group: low dose (3 mg/kg), high dose (9 mg/kg), and placebo (0 mg/kg) and these will be used for the "treatment groups" in the analysis.

AUC values with corresponding covariance matrix will be determined by modeling the $\log_{10}$ viral load values over time using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within subject errors over time. The Kenward-Roger method will be used to approximate the degrees of freedom.

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 the Type I error rate. A dose-response trend is established when the maximum of the *t*-test statistics exceeds the critical value.

Secondary Endpoints

Antiviral Activity

The other antiviral endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented. Kaplan-Meier Curves will be produced to graphically describe the time to event data.

Differences between treatment groups in viral load will be derived from the same model as for the primary endpoint using appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals (CIs). Other covariates as well as interaction effects might also be investigated.

The time to undetectable RSV viral load will be analyzed using Kaplan-Meier plots and will be modeled using an accelerated failure time model, adjusted for covariates, such as strata and baseline viral load, to estimate differences between treatment groups. A generalized MCP-Mod approach will be used to test for existence of dose-response, if applicable.

More details regarding the analysis of these data will be described in the SAP.

Clinical Course of RSV Infection

All endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented.

Time to-variables (eg, time to resolution of symptoms, time to clinical stability, length of hospital stay) will be analyzed using Kaplan-Meier plots and will be modeled using an accelerated failure time model, adjusted for covariates, such as strata and baseline viral load, to estimate differences between treatment groups. 80% and 95% 2-sided CIs will be calculated. A generalized MCP-Mod approach defined will be used to test for existence of dose-response.

Parent(s)/caregiver(s) PRESORS and clinician PRESORS scores will be descriptively summarized by treatment group and compared between treatment groups. 80% and 95% 2-sided CIs will be calculated. A generalized MCP-Mod approach will be used to test for existence of dose-response on parent(s)/caregiver(s) PRESORS and clinician PRESORS scores.

More details regarding the analysis of these data will be described in the SAP.

Correlation Between Antiviral Effect and Clinical Course Endpoints

Selected antiviral effect and clinical course endpoints will be subjected to correlation analysis. Various approaches, including graphical analysis, regression methods but also longitudinal analyses will be utilized.

More details regarding the analysis of these data will be described in the SAP.

Viral Sequencing

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

Safety Analysis

Safety data will be presented descriptively. Statistical testing of safety data, if appropriate, may be presented in a separate report.

For safety, baseline is defined as the last assessment prior to the first intake of study drug.

The population for the safety analysis will consist of all randomized subjects who received at least 1 dose of study drug.

Pharmacokinetic Analysis

Population PK analysis of concentration-time data of JNJ-53718678 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Relationships

Relationships of JNJ-53718678 population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored. These relationships will be presented in a tabular and/or graphical display.

Medical Resource Utilization Analysis

Medical resource utilization will be descriptively summarized by treatment group.

Acceptability and Palatability Analysis

Data on acceptability and palatability of the JNJ-53718678 formulation will be presented descriptively.

Biomarker Analysis

Analyses may be performed at the sponsor's discretion and reported separately from this study. Statistical approaches to explore correlations between clinical outcome, viral load, and biomarkers in blood and mid-turbinate nasal swabs vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences among study subjects.

Other Analyses

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

Independent Data Monitoring Committee

An IDMC will be established to monitor and review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review safety data and results from interim analyses. After the review, the IDMC will provide recommendations to the Sponsor Committee.

The IDMC will also review the safety and PK data from 6 subjects in the subcohort of Cohort 1 and the interim analysis 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 recommendations from the IDMC.

TIME AND EVENTS SCHEDULE

COHORT 1

During Hospitalization

Phase	Screening	Treatment Phase					Follow-up[a]					
Day	**-1 to 1[b]**	**1**	**2[d]**	**3**	**4-7**	**8**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
	Screening / Predose											**Phone follow-up/ Conditional[c] on-site visit**
Study Procedures												
Screening/Administrative												
Informed Consent	X											
Diagnostic ICF (optional)[e]	X											
Eligibility criteria[f]	X											
Subject characteristics and demographics	X											
Medical history/prior medications	X											
Local assay for RSV diagnosis[g]	X											
Randomization		X[h]										
Study Drug Administration												
Dosing study medication[i]		X	X	X	X							
Provision of study drug for daily use at home at discharge[j]			(X)	(X)	(X)							
Efficacy Assessments												
Clinical evaluation[k]	X	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	bid	bid		(X)[m]
Clinician PRESORS[n]	X	bid	bid	bid	bid	bid	bid	bid	X	X		
Parent(s)/caregiver(s) PRESORS[o]	X	bid	bid	bid	bid	bid	bid	bid	X	X[p]		

Phase	Screening	Treatment Phase					Follow-up[a]					
Day	**-1 to 1[b]**	**1**	**2[d]**	**3**	**4-7**	**8**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
	Screening / Predose											**Phone follow-up/ Conditional[e] on-site visit**
Monitoring of parent(s)/caregiver(s) PRESORS completion by the site staff	X	X	X	X	X	X	X	X	X	X		
Mid-turbinate nasal swab: RSV diagnosis confirmation, RSV viral load, presence of other viral or bacterial pathogens, viral sequencing (centrally)[q,r,s]	X[t]											
Mid-turbinate nasal swab: RSV viral load, viral sequencing[r,s]			X	X	X	X	X	X		X		
Nasopharyngeal and/or tracheal aspirate sample for RSV RNA viral load determination (centrally)[u]	X		X	X	X	X	X	X		X		
Medical resource utilization	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments												
Systolic and diastolic blood pressure[v]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid		(X)[m]
Complete physical examination (all body systems)[w]	X											
Directed physical examination[x]				X		X		X		X		(X)[m]
ECG (triplicate 12-lead)[y]	X					X				X		(X)[m]

Phase	Screening	Treatment Phase					Follow-up[a]					
Day	**-1 to 1[b]**	**1**	**2[d]**	**3**	**4-7**	**8**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
	Screening / Predose											**Phone follow-up/ Conditional[c] on-site visit**
Clinical Laboratory Assessments												
Blood sampling for hematology and biochemistry[z]	X					X				X		(X)[m]
Urinalysis[aa]	X					X				X		(X)[m]
Pharmacokinetic												
Blood sampling for pharmacokinetics of JNJ-53718678[bb]		X	X									
Acceptability/Palatability												
Acceptability/ palatability questionnaire for parent(s)/caregiver(s)						X						
Ongoing Subject Review												
Adverse events[cc]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	(X)[m]

a. In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

b. Screening/predose assessments can only start after signing of the ICF and before randomization. All screening/predose procedures should take place prior to the first study drug intake. If needed, and depending on the time of hospital admission, screening/predose assessments and establishment of eligibility can continue the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility. For analysis purposes, the day of first study drug intake will be considered Day 1.

c. Subject's parent(s)/caregiver(s) will be contacted by site staff for a telephone follow up visit. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 Follow-Up Visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit.

d. Subjects can be discharged as of Day 2, if deemed appropriate by the investigator and after completion of the required investigator-performed assessments for that day, with exception of the evening bid assessments.

e. Prior to signing the main consent form for the study, subject's legally acceptable representative may specifically allow for the collection and testing of nasal mid-turbinate swab by signing the pre-screening (diagnostic) ICF. This is not required if a positive RSV diagnostic result based on a local SOC sample collected within 48 hours prior to anticipated randomization is available and used for determining study eligibility.
f. Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
g. During screening, a study-specific screening sample (mid-turbinate swab) will be collected for the local diagnosis of RSV infection using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main study ICF or with the diagnostic ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.
h. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first. Randomization is to occur predose.
i. Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day. The study drug can be administered with/without food. The study drug will be administered orally using a dosing syringe. The drug can also be administered through a nasogastric tube, if already in place.
j. Study site personnel will instruct subjects' parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing. Study drug will be provided at day of discharge in 1 single vial, from which the assigned volume is to be withdrawn each day, for the remainder of the treatment period.
k. Clinical evaluation includes measurements/evaluations of respiratory rate, heart rate, body temperature, and SpO_2, occurrence of complications, need for antibiotics, oxygen requirement (type and duration), level of and duration of hospital care, duration of hospitalization, hydration/feeding by IV line/nasogastric tube. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. All clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding).
l. If the subject is enrolled in the substudy of Study 53718678RSV2002 (see Section 3.1), the same parameters as assessed by the biosensor will be recorded from the standard-of-care monitoring/assessments as part of the substudy assessments (refer to the substudy Clinical Protocol for detailed information).
m. Only applicable in case of on-site visit.
n. The clinician PRESORS (Attachment 4) has to be completed by the clinician on the electronic device.
o. An electronic device will be provided to the subject's parent(s)/caregiver(s) during screening and the investigator/study site personnel will provide sufficient information to enable the subject's parent(s)/caregiver(s) to complete these assessments. The first parent(s)/caregiver(s) PRESORS (Attachment 5) assessment of the bid schedule on Day 1 needs to be completed as close as feasible and prior to the first administration of the study drug. Detailed information is available in Section 9.2.2.
p. The parent(s)/caregiver(s) PRESORS has to be completed by the subject's parent(s)/caregiver(s) during end-of-study visit as the first activity of the visit prior to any other procedures.
q. One mid-turbinate nasal swab will be taken of which aliquots will be used for the central laboratory confirmation of RSV infection, to determine RSV viral load, to determine mutations in the viral genome potentially associated with resistance to JNJ-53718678, and to determine the presence of other viral or bacterial pathogens.
r. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Swabs will be collected each day during hospitalization through Day 13 or until discharge (whichever comes first), and on Day 14 and Day 21 (if still hospitalized). Detailed information on sample collection is available in Section 9.2.1.
s. Leftover mid-turbinate nasal swab samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.

t. The baseline mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study drug (on Day 1). If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL each). If feasible, the nasopharyngeal and/or tracheal aspirate sample should be collected as close as possible and prior to the first administration of study drug (on Day 1).
u. Nasopharyngeal and/or tracheal aspirate samples will be collected when aspiration of nasopharyngeal and/or tracheal secretions is performed as part of routine clinical care while hospitalized (ie, at selected sites only) to assess RSV RNA viral load centrally.
v. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
w. Physical examination of all body systems includes length and head circumference and body weight measurement and skin examination.
x. Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.
y. Triplicate 12-lead ECGs will be obtained, approximately 1 minute apart and preferably all within 5 minutes. ECGs may be repeated at the discretion of the investigator. ECGs will be obtained in a supine position after 5 minutes of rest. If an ECG is scheduled at the same timepoint as other assessments, the ECG should be performed first.
z. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor. Subjects can start treatment before the laboratory results are available (see also Section 9.1.2).
aa. Urinalysis will be performed using dipsticks provided by the central laboratory. In case of abnormalities, the urine sample will be shipped to the central laboratory for flow cytometric and/or microscopic evaluation(s).
bb. Blood samples for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick. 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 (see Table 2). 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 (see Table 2). 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 at this site. Detailed information on sample collection is available in Section 9.4.1. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.
cc. Adverse events related to the use of the biosensor reported during the substudy will be recorded in the eCRF of the main study.

COHORT 1

After Discharge[a]

Phase	Treatment Phase						Follow-up[b]					
Day	**2**	**3**	**4**	**5 (±1)**	**6-7**	**8 (+1)**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
		On-site visit[c]		**On-site visit[c]**		**On-site visit[c]**		**On-site visit[c]**		**On-site visit[c]**		**Phone follow-up/ Conditional[d] On-site visit[c]**
Study Procedures												
Study Drug Administration												
Dosing study medication and document dosing in study medication log[e]		X	X	X	X							
Efficacy Assessments												
Clinical evaluation[f]		X[g]		X[g]		X[g]		X[g]		X		(X)[h]
Clinician PRESORS[i]		X		X		X		X		X		
Parent(s)/caregiver(s) PRESORS[j]	bid[k]	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	bid[l]	X	X[m]		
Monitoring of parent(s)/caregiver(s) PRESORS completion by the site staff	X	X	X	X	X	X	X	X	X	X		
Mid-turbinate nasal swab: RSV viral load, viral sequencing (centrally)[n,o]		X	X	X	X	X	X	X		X		
Nasal swab log[p]			X		X		X					
Temperature log[q]	X[r]	bid	bid	bid	bid	bid	bid	bid	X	X		
Medical resource utilization		X	X	X	X	X	X	X	X	X	X	X
Safety Assessments												
Systolic and diastolic blood pressure[s]		X		X		X		X		X		(X)[h]

Phase	Treatment Phase						Follow-up[b]					
Day	**2**	**3**	**4**	**5 (±1)**	**6-7**	**8 (+1)**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
		On-site visit[c]		**On-site visit[c]**		**On-site visit[c]**		**On-site visit[c]**		**On-site visit[c]**		**Phone follow-up/ Conditional[d] On-site visit[c]**
Directed physical examination[u]		X				X		X		X		(X)[h]
ECG (triplicate 12-lead)[v]						X				X		(X)[h]
Clinical Laboratory Assessments												
Blood sampling for hematology and biochemistry[w]						X				X		(X)[h]
Urinalysis[x]						X				X		(X)[h]
Acceptability/Palatability												
Acceptability/palatability questionnaire for parent(s)/caregiver(s)						X						
Ongoing Subject Review												
Adverse events[y]		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X	X	(X)[h]

a. When subjects are rehospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the TIME AND EVENTS SCHEDULE, if practically feasible.

b. In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

c. If feasible for the study site and if allowed per local regulations, home visits are allowed instead of on-site visits (although on-site visits are preferred).

d. Subject's parent(s)/caregiver(s) will be contacted by site staff for a telephone follow up visit. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 Follow-Up Visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit for the subject at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28 (±3). Only clinically relevant assessments will be performed during this visit.

e. The study drug can be administered with/without food. The study drug will be administered orally using a dosing syringe.

f. Clinical evaluation includes measurements/evaluations of respiratory rate, heart rate, body temperature, and SpO_2, need for and duration of rehospitalization, occurrence of complications, need for antibiotics. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving

antipyretics. Parents/caregivers should be instructed accordingly. All clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding).

g. If the subject is enrolled in the substudy of Study 53718678RSV2002 (see Section 3.1), the same parameters as assessed by the biosensor will be recorded from the standard-of-care monitoring/assessments as part of the substudy assessments (refer to the substudy Clinical Protocol for detailed information).
h. Only applicable in case of on-site visit.
i. The clinician PRESORS (Attachment 4) has to be completed by the clinician on the electronic device.
j. Detailed information is available in Section 9.2.2.
k. The morning assessment needs to be done prior to discharge and the evening one should be done at home.
l. If the subject is discharged prior to completion of the last assessment of the bid schedule, this last assessment should be performed at home.
m. The parent(s)/caregiver(s) PRESORS (Attachment 5) has to be completed by the subject's parent(s)/caregiver(s) during end-of-study visit as the first activity of the visit prior to any other procedures.
n. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). After discharge, swabs will be collected daily through Day 8 in all subjects. As of Day 8, in subjects who were symptomatic based on the clinician PRESORS at Day 8, daily swabs will be collected through Day 13 or until the subject becomes asymptomatic based on the parent(s)/caregiver(s) PRESORS, as evaluated by the investigational staff (whichever comes first). On Day 14 and Day 21, a swab will be collected during the scheduled visit for all subjects. Detailed information on sample collection is available in Section 9.2.1.
o. Leftover mid-turbinate nasal swab samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.
p. To be completed by parent(s)/caregiver(s) on the electronic device (see Attachment 7 [nasal swab log]), if applicable. Refer to Section 9.2.1 for detailed information.
q. Body temperature to be measured by parent(s)/caregiver(s) and recorded on the electronic device (see Attachment 8 [temperature log]). In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parents/caregivers should be instructed accordingly.
r. On the day of discharge, if discharged in the morning, only the evening assessment of the bid schedule should be recorded in the temperature log on the electronic device.
s. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
t. Physical examination of all body systems includes length and head circumference and body weight measurement and skin examination.
u. Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.
v. Triplicate 12-lead ECGs will be obtained, approximately 1 minute apart and preferably all within 5 minutes. ECGs may be repeated at the discretion of the investigator. ECGs will be obtained in a supine position after 5 minutes of rest. If an ECG is scheduled at the same timepoint as other assessments, the ECG should be performed first.
w. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.
x. Urinalysis will be performed using dipsticks provided by the central laboratory. In case of abnormalities, the urine sample will be shipped to the central laboratory for flow cytometric and/or microscopic evaluation(s).
y. Adverse events related to the use of the biosensor reported during the substudy will be recorded in the eCRF of the main study.

Note: Additional unscheduled visits in case of lab abnormalities, ECG abnormalities, need for clinical follow-up of (an) AE(s) can be scheduled at the discretion of the investigator.

COHORT 2 SUBJECTS RECRUITED AFTER PROTOCOL AMENDMENT 4[a]

Phase	Screening	Treatment Phase							Follow-up[b]					
Day	-1 to 1[c]	1	2	3	4	5 (±1)	6-7	8 (+1)	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3) End-of-study
	Screening / Predose On-site	Treatment On-site		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		Phone visit/ Conditional[e] On-site visit[d]
Study Procedures														
Screening/Administrative														
Informed Consent	X													
Diagnostic ICF (optional)[f]	X													
Eligibility criteria[g]	X													
Subject characteristics and demographics	X													
Medical history/prior medications	X													
Local assay for RSV diagnosis[h]	X													
Randomization		X[i]												
Study Drug Administration														
Dosing study medication[j]		bid	bid	bid	bid	bid	bid							
Provision of study drug for daily use at home[k]		X												
Document dosing in study medication log		bid[l]	bid	bid	bid	bid	bid							
Checking of study medication log		X	X	X	X	X	X							
Efficacy Assessments														
Clinical evaluation[m]	X	X		X[n]		X[n]		X[n]		X[n]		X		(X)[o]

Phase	Screening	Treatment Phase							Follow-up[b]					
Day	-1 to 1[c]	1	2	3	4	5 (±1)	6-7	8 (+1)	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3) End-of-study
	Screening / Predose On-site	Treatment On-site		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		Phone visit/ Conditional[e] On-site visit[d]
Clinician PRESORS[p]	X	X		X		X		X		X		X		
Parent(s)/ caregiver(s) PRESORS[q]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid	X	X[r]		
Monitoring of parent(s)/caregiver(s) PRESORS completion by the site staff	X	X	X	X	X	X	X	X	X	X	X	X		
Mid-turbinate nasal swab: RSV diagnosis confirmation, RSV viral load, presence of other viral or bacterial pathogens, viral sequencing (centrally)[s,t,u]	X[v]													
Mid-turbinate nasal swab: RSV viral load, viral sequencing[t,u]			X	X	X	X	X	X	X	X		X		
Nasal swab log[w]			X		X		X		X					
Temperature log[x]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid	X	X		
Medical resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments														
Systolic and diastolic blood pressure[y]	X			X		X		X		X		X		(X)[o]
Physical examination (all body systems)[z]	X													
Directed physical examination[aa]				X				X		X		X		(X)[o]

Phase	Screening	Treatment Phase							Follow-up[b]					
Day	-1 to 1[c]	1	2	3	4	5 (±1)	6-7	8 (+1)	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3) End-of-study
	Screening / Predose On-site	Treatment On-site		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]		Phone visit/ Conditional[e] On-site visit[d]
ECG (triplicate 12-lead)[bb]	X	X[gg]		X[gg]				X				X[gg]		(X)[o,gg]
Clinical Laboratory Assessments														
Blood sampling for hematology and biochemistry[cc]	X[hh]							X[hh]				X		(X)[o]
Urinalysis[dd]	X							X				X		(X)[o]
Pharmacokinetics														
Blood sampling for pharmacokinetics of JNJ-53718678[ee]		X[ii]		(X)[ii]		(X)[ii]								
Acceptability/Palatability														
Acceptability/ palatability questionnaire for parent(s)/caregiver(s)								X						
Ongoing Subject Review														
Adverse events[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[o]

a. When subjects are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the TIME AND EVENTS SCHEDULE, if practically feasible.

b. In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

c. Screening/predose assessments can only start after signing of the ICF and before randomization. All screening/predose procedures should take place prior to the first study drug intake.

d. If feasible for the study site and if allowed per local regulations, home visits are allowed instead of on-site visits (although on-site visits are preferred).

e. Subject's parent(s)/caregiver(s) will be contacted by site staff for a telephone follow up visit. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 follow-up visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator,

to have a Safety Follow-up Visit for the subject at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28 (±3). Only clinically relevant assessments will be performed during this visit.

f. Prior to signing the main consent form for the study, subject's legally acceptable representative may specifically allow for the collection and testing of nasal mid-turbinate swab by signing the pre-screening (diagnostic) ICF. This is not required if a positive RSV diagnostic result based on a local SOC sample collected within 48 hours prior to anticipated randomization is available and used for determining study eligibility.

g. Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.

h. During screening, a study-specific screening sample (mid-turbinate swab) will be collected for the local diagnosis of RSV infection using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main study ICF or with the diagnostic ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.

i. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first. Randomization is to occur predose.

j. Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. The study drug can be administered with/without food. The study drug will be administered orally using a dosing syringe.

k. Study site personnel will instruct subjects' parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing. Study drug will be provided in 1 single vial, from which the assigned volume is to be withdrawn each day.

l. Date and time of study medication dosing has to be recorded, also in case if it cannot be recorded in the study medication log by the site.

m. Clinical evaluation includes measurements/evaluations of respiratory rate, heart rate, body temperature, and SpO_2, need for and duration of hospitalization, occurrence of complications, need for antibiotics. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parents/caregivers should be instructed accordingly. All clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding). In case Cohort 2 Screening and Randomization occur on the same calendar day, clinical evaluation does not have to be repeated.

n. If the subject is enrolled in the substudy of Study 53718678RSV2002 (see Section 3.1), heart rate, respiratory rate, and SpO_2 will be recorded as part of the substudy assessments (refer to the substudy Clinical Protocol for detailed information).

o. Only applicable in case of on-site visit.

p. The clinician PRESORS (Attachment 4) has to be completed by the clinician on the electronic device.

q. An electronic device will be provided to the subject's parent(s)/caregiver(s) during screening and the investigator/study site personnel will provide sufficient information to enable the subject's parent(s)/caregiver(s) to complete these assessments. The first parent(s)/caregiver(s) PRESORS (Attachment 5) assessment of the bid schedule on Day 1 needs to be completed as close as feasible and prior to the first administration of study drug. Detailed information is available in Section 9.2.2.

r. The parent(s)/caregiver(s) PRESORS has to be completed by the subject's parent(s)/caregiver(s) during end-of-study visit as the first activity of the visit prior to any other procedures.

s. One mid-turbinate nasal swab will be taken of which aliquots will be used for the central laboratory confirmation of RSV infection, to determine RSV viral load, to determine mutations in the viral genome potentially associated with resistance to JNJ-53718678, and to determine the presence of other viral or bacterial pathogens.

t. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Swabs will be collected daily through Day 8 in all subjects. The investigator/study site personnel will train the parent(s)/caregiver(s) to collect the mid-turbinate nasal swab in case collection by an HCP is not possible. As of Day 8, in subjects who were symptomatic based on the clinician PRESORS at Day 8, daily swabs will be collected through Day 13 or until the subject becomes asymptomatic based on the parent(s)/caregiver(s) PRESORS, as evaluated by the investigational staff (whichever comes first). On Day 14 and Day 21, a swab will be collected during the scheduled visit for all subjects. Detailed information on sample collection is available in Section 9.2.1.
u. Leftover mid-turbinate nasal swab samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.
v. The baseline mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study drug (on Day 1). If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL).
w. To be completed by parent(s)/caregiver(s) on the electronic device (see Attachment 7 [nasal swab log]), if applicable. Refer to Section 9.2.1 for detailed information.
x. Body temperature to be measured by parent(s)/caregiver(s) and recorded on the electronic device (see Attachment 8 [temperature log]). In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parents/caregivers should be instructed accordingly.
y. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
z. Complete physical examination of all body systems includes length and head circumference and body weight measurement and skin examination.
aa. Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.
bb. Triplicate 12-lead ECGs will be obtained, approximately 1 minute apart and preferably all within 5 minutes. ECGs may be repeated at the discretion of the investigator. ECGs will be obtained in a supine position after 5 minutes of rest. If an ECG is scheduled at the same timepoint as other assessments, the ECG should be performed first.
cc. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor. Subjects can start treatment before the laboratory results are available (see also Section 9.1.2).
dd. Urinalysis will be performed using dipsticks provided by the central laboratory. In case of abnormalities, the urine sample will be shipped to the central laboratory for flow cytometric and/or microscopic evaluation(s).
ee. Blood samples for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick on Days 3 and 5 at a random timepoint (predose or postdose) during the visit. Detailed information on sample collection is available in Section 9.4. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at discretion of the sponsor.
ff. Adverse events related to the use of the biosensor reported during the substudy will be recorded in the eCRF of the main study.
gg. At Day 1 and Day 3, ECGs should be obtained approximately one hour after administration of study drug. At Day 28, ECGs should be obtained in case abnormal ECGs at Day 21 or at discretion of the principal investigator. Anytime when it is clinically indicated or for confirmation of abnormal ECG findings, unscheduled ECGs should be obtained.
hh. Levels of potassium and magnesium will be determined by the central laboratory. In case of hypokalemia or hypomagnesemia at screening or at Day 8, the levels of potassium and magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) may be required.
ii. PK samples should be collected approximately one hour after administration of study drug (after the ECGs are obtained if applicable) at Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

Note 1: *Additional unscheduled visits in case of lab abnormalities, ECG abnormalities, need for clinical follow up of (an) AE(s) can be scheduled at the discretion of the investigator.*
Note 2: *Refer to Attachment 10 for guidance on study conduct during the COVID 19 pandemic.*

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AUC	area under the RSV viral load-time curve
BCRP	breast cancer resistance protein
bid	twice daily
BM	bone marrow
BW	body weight
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
COVID-19	Coronavirus Disease 2019
CPE	complete physical examination
(e)CRF	case report form(s) (paper or electronic as appropriate for this study)
CV	coefficient of variation
CYP	cytochrome
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
DPE	directed physical exam
EC_{50}	effective concentration for 50% inhibition
ECG	electrocardiogram
eDC	electronic data capture
FC	food consumption
GCP	Good Clinical Practice
GGT	γ-glutamyltransferase
GLP	Good Laboratory Practice
GPT	glutamic-pyruvic transaminase
HCP	healthcare provider
HIV	human immunodeficiency virus
HP-β-CD	2-Hydroxypropyl-beta-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IPPI	investigational product preparation instruction
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LLOQ	lower limit of quantification
LRTI	lower respiratory tract infection
MATE1	multidrug and toxin extrusion 1
MCP-Mod	Multiple Comparison Procedure-Modeling
MDE	multiple-dose escalation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic-anion-transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PND	post-natal day
popPK	population pharmacokinetic(s)
PQC	Product Quality Complaint
PRESORS	Pediatric RSV Electronic Severity and Outcome Rating Scales
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PT	prothrombin time
qd	once daily
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTcI	individual-corrected QT interval
RBC	red blood cell
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SDE	single-dose escalation
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TQT	thorough QT
URTI	upper respiratory tract infection
WBC	white blood cell

1. INTRODUCTION

Respiratory syncytial virus (RSV), a negative-stranded ribonucleic acid virus belonging to the *Pneumoviridae* family, is considered the most important virus causing acute lower respiratory tract infection (LRTI). Two subtypes of RSV have been identified ie, subtypes A and B that generally co-circulate simultaneously, although with a higher prevalence of subtype A.[8] The RSV season occurs during winter months in regions with temperate climates in the Northern and Southern Hemispheres and throughout the year or with peaks semi-annually in tropical regions.[1,30]

In most patients, RSV usually results in upper respiratory tract infections eliciting "common cold"-like symptoms, which might last up to 2 weeks and are usually self-limiting but hospitalization does occur, with hospitalizations in the United States for RSV estimated at 55.3/100,000 person-years between 1993 and 2008 for all ages.[31] RSV infection can cause considerable morbidity and mortality in certain patient populations such as infants[22] where RSV can lead to lower respiratory tract infection (LRTI), with severe respiratory compromise. In children ≤3 years of age, the clinical presentation of RSV disease is linked to the anatomy of their maturing respiratory tract. RSV infection causes inflammation and necrosis of the bronchiolar epithelial cells. The lumina of the bronchioles become obstructed from edema of the airway wall, increased mucus secretion, sloughed epithelium, and cellular debris. The small-diameter airways in infants are particularly vulnerable to obstruction. Such obstruction of bronchioli may lead to bronchiolitis and can cause respiratory distress.[20,21]

RSV is a major cause of hospital admissions and death in young children worldwide.[22,25] Infants born prematurely or close to the RSV season and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI.[9] In 2015, there were approximately 33.1 million RSV-LRTI episodes in 0 4-year-old children globally, which resulted in approximately 3.2 million hospitalizations and 59,600 deaths for this age group. Approximately 45% of these hospital admissions and in-hospital deaths occurred in children younger than 6 months.[26]

On the other hand, among children <5 years of age with RSV infection, 97.7% present for medical care as outpatients in emergency departments and in pediatric practices, while 2.7% require hospitalization.[11] It has been estimated that 2.2% (1.7 million visits) of all US primary care visits of children <5 years of age in the year 2000 resulted from RSV infection.[18] These rates of visits for RSV-associated acute respiratory infections suggest that a major proportion of the burden of RSV results in outpatient visits among children beyond infancy.[11]

Despite the large medical and economic burden, no vaccines or antiviral agents have been approved for the prevention or treatment of RSV infection in either adult or pediatric populations.[2,24]. In hospitalized patients, the current treatment of RSV infection is often limited to supportive care, consisting of supplemental oxygen therapy, nutrition, fluids, and, in some cases, mechanical ventilation.[7,28] In an outpatient setting, the standard of care is limited to symptomatic treatment of the flu-like manifestations of the disease. Overall, the unmet medical need (prophylactically and therapeutically) is substantial in both children and adults with RSV infection, whether hospitalized or outpatients.

The window between the onset of clinical symptoms after RSV exposure followed by infection (Day 3) and peak viral load (Day 6) is on average 3 days in children and adults[4,5,6], which is sufficiently long to initiate treatment, if diagnosed early. As most hospitalized subjects with RSV infection already had presented to a primary healthcare provider (HCP) 1 or 2 days prior to hospitalization[6,29], there is indeed an opportunity to initiate treatment in these subjects in a community setting ie, at the point of the initial HCP contact. Also, studies in the adult and pediatric population have demonstrated that RSV viral load and severity of disease symptoms are closely correlated,[4,5,6] except for 1 recent study that did not confirm this correlation.[27] Together, these data suggest early initiation of treatment in outpatients is possible, and could result in a decrease of the viral load, syncytia formation, and in inflammatory reactions following RSV infection, and hence may improve disease outcomes and shorten the duration and/or severity of the disease, potentially avoiding hospitalization.

Enveloped viruses like RSV have a complex membrane fusion machinery that includes a fusion protein that enables the deposition of the viral nucleic acid genome into the host cells and initiates their replication.[3,19] JNJ-53718678 is an investigational RSV specific fusion inhibitor belonging to the indole chemical class and is under development for the treatment of RSV infection. The study drug shows in vitro activity against a panel of viruses belonging to both the RSV subfamilies A or B. In addition, antiviral activity of JNJ-53718678 was demonstrated during clinical studies in healthy adults inoculated with RSV (Study 53718678RSV2001) and in pediatric subjects hospitalized due to RSV-infection (Study 53718678RSV1005).

For the most comprehensive nonclinical and clinical information regarding JNJ-53718678, refer to the latest version of the Investigator's Brochure (IB) and Addendum for JNJ-53718678.[17,16]

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

1.1. Background

Nonclinical Studies

Nonclinical Pharmacology

The in vitro effective concentration for 50% inhibition (EC_{50}) of RSV was found to be 0.23 ng/mL (460 pM) as measured in a cellular infectious assay. The in vivo EC_{50} was 75 ng/mL (150 nM) or 81 ng/mL (160 nM) when the reduction of RSV titer was analyzed in bronchoalveolar fluid or lavaged-lung tissue, respectively, from cotton rats that received a single dose of different concentrations of JNJ-53718678, 1 hour before infection. Further efficacy and mechanism of action studies demonstrated that JNJ-53718678 is a selective and extremely potent small-molecule RSV fusion inhibitor, capable of significantly reducing the viral titer. Concurrently, a decrease of the virus-induced pro-inflammatory response was observed in RSV-infected and JNJ-53718678 treated Balb/C mice. Finally, once daily (qd) oral treatment of RSV-infected neonatal lambs with 1-, 5-, and 25-mg/kg doses of JNJ-53718678 resulted in significant concentration-dependent reductions of the viral titer in both bronchoalveolar lavage fluid (BALF) as well as lavaged-lung tissue as compared to animals that received vehicle only. There were no differences between

treatment groups for heart rate, respiratory rate, and temperature. Signs of "illness" (including abnormal lung sounds, as of Day 1 after inoculation) and/or eye and nasal discharges (as of Day 4 after inoculation) were only observed in the vehicle-treated animals and not in the animals receiving JNJ-53718678 treatment. Estimated EC_{50} for the average plasma concentration at steady state was 753 ng/mL and 296 ng/mL for BALF and lung, respectively, again indicating a potent antiviral activity. In addition, a dose-dependent reduction of the production of several RSV-induced pro-inflammatory cytokines and chemokines (ie, interferon [IFN]-γ-induced protein-10 [IP-10], monocyte chemotactic protein-1 [MCP-1], macrophage inflammatory protein-1α [MIP-1α], and IFN-λ), RSV-induced gross lung lesion formation and concomitantly, significant improvement of the general lung condition was observed (eg, reduction of bronchiolitis and lung neutrophilia). Together, these results demonstrate the efficacy of the study drug to inhibit RSV-induced lung pathology sequelae.

No in vitro antiviral activity was observed for the JNJ-53718678 metabolites M12 (JNJ-53541683), M19 (JNJ-64564071), and M37 (JNJ-69101045); the EC_{50} value for M5 (JNJ-54172794) was 7.7 nM.

In high-throughput screening (HTS) ion channel voltage clamp assays, JNJ-53718678 did not affect cardiac sodium membrane current (I_{Na}) up to 10 μM, but slightly to markedly inhibited cardiac potassium membrane current (I_{Kr}) at concentrations starting at 1 μM. In a Good Laboratory Practice (GLP) human-ether-a-gogo-related (hERG) gene study, with JNJ-53718678, the I_{Kr}-blocking liability was confirmed, and a 50% inhibition concentration (IC_{50}) of 1.9 μM was estimated. In addition, slight inhibition of the hERG mediated IKr was present at 10 μM M5, but not at 1 and 3 μM. When JNJ-53718678 was administered IV to anesthetized female guinea pigs, no significant cardiovascular effects were induced up to the 10-mg/kg dose (cumulative dose: 19.69 mg/kg; median plasma exposure: 7,580 ng/mL). In a first study in male conscious dogs, no notable effects were found on the cardiovascular and respiratory parameters up to an oral JNJ-53718678 dose of 100 mg/kg (mean JNJ-53718678 peak plasma exposure: 4,270 ng/mL). After single JNJ-53718678 doses of 75 and 250 mg/kg and 5-day repeated JNJ-53718678 doses of 250 mg/kg qd in conscious dogs, heart rates (HR) were increased at all doses in most dogs and blood pressure (BP) was decreased at all dosing occasions in all dogs. Respiratory parameters were not affected. Mean peak plasma exposure values of JNJ-53718678 after a single JNJ-53718678 dose of 75 mg/kg were 15,400 ng/mL, while they amounted to 31,000 ng/mL after giving repeated JNJ-53718678 doses of 250 mg/kg qd for 5 days.

Evaluation of neurofunctional integrity of rats revealed minimally and transiently decreased neuromuscular function, next to minimal effects related to gastrointestinal function, at single JNJ-53718678 doses of 150 and 1,500 mg/kg in rats. There were no effects at the single JNJ-53718678 dose of 25 mg/kg (maximum plasma concentration [C_{max}] 826 ng/mL; area under the plasma concentration-time curve from 0 to 7 hours [$AUC_{0\ 7h}$] 3,380 ng.h/mL).

Pharmacokinetics and Product Metabolism in Animals

Following single IV administration to different preclinical species, JNJ-53718678 clearance (CL) was high in rats (>100% of hepatic blood flow) and moderate in mice, dogs, and monkeys (~30%

of hepatic blood flow). The volume of distribution at steady state was moderate in all species (1-3 L/kg).

Following single oral administration of JNJ-53718678, absorption from the gastrointestinal tract was rapid in all preclinical species. Mean oral bioavailability was variable across preclinical species and ranged from 18% (monkey) to 90% (dog). JNJ-53718678 plasma exposure (C_{max}, AUC) increased more than dose-proportionally in male rats and close to dose-proportionally in monkeys at low doses up to 10 and 5 mg/kg, respectively. Feeding status had minimal to no impact on oral bioavailability of solution and suspension formulations at 5 mg/kg in dogs.

Following repeated oral administration of JNJ-53718678, plasma exposure was higher in female than in male rats, while no gender difference in JNJ-53718678 exposure was observed in dogs. JNJ-53718678 plasma exposure decreased upon repeated dosing in rats, indicating clearance auto-induction, and increased in dogs and minipigs. These changes in exposure upon repeated dosing in rats were observed at the mid to high doses tested in the toxicity studies and were minor or not seen at the lowest dose (25 mg/kg/day).

Following single oral administration of JNJ-53718678 to juvenile preclinical species (1 day of age), JNJ-53718678 plasma exposure was lower than in adult animals in rats and higher in minipigs and dogs at the same dose levels.

In rats, upon 3-week repeated dosing from 1 to 21 days of age (pilot study), exposure increased at low and mid doses (25 and 100 mg/kg) during the first week of dosing, while no consistent change in exposure was observed throughout administration at the high dose (200 mg/kg). Four-weeks of repeated dosing in juvenile rats (starting on post-natal day [PND] 4; GLP study) resulted in a more than dose-proportional increase in exposure parameters, with C_{max} and AUC between 50 and 150 mg/kg/day and a less than dose-proportional increase between 150 and 400 mg/kg/day. In minipigs and dogs (pilot studies), exposure increased upon repeated dosing during the first week of dosing at all doses. Five-weeks of repeated dosing in juvenile minipigs (starting on PND1; GLP study) resulted in rather flat plasma concentration-time profiles. Exposure values increased generally more than dose-proportionally over the studied dose range (5-25 mg/kg/day). Exposure was lower at the end versus the start of the dosing period at 5 mg/kg/day, but remained fairly similar at 10 and 25 mg/kg/day.

Plasma protein binding of JNJ-53718678 amounted to 88% to 99% in adult preclinical species, 94% in adult humans and 92% to 93% in juvenile preclinical species. JNJ-53718678 binds preferentially to alfa-1-acid glycoprotein (α-1-AGP). Following single oral administration of JNJ-53718678 to male Sprague-Dawley rats, the tissue concentration-time profiles of unchanged JNJ-53718678 showed a pattern similar to the plasma profile with fast distribution to tissues and parallel concentration decline. Distribution was moderate in most tissues (tissue-to-plasma AUC ratio ranging from 2 in muscle to 14 in liver), and low in the brain (brain-to-plasma AUC ratio: 0.1). The lung-to-plasma ratio of JNJ-53718678 was 3.5. In male cotton rats, the concentration of JNJ-53718678 in lung epithelial lining fluid 1 hour after single oral administration at 100 mg/kg was estimated to be about 1.5-fold higher than the corresponding plasma concentration. In a quantitative whole-body autoradiography (QWBA) study in male pigmented rats, maximum

concentrations of total radioactivity in most tissues and in plasma were measured at 24 hours after the single oral administration of ^{14}C-JNJ-53718678. In the majority of tissues, total radioactivity concentrations were higher than in whole blood. Tissue-to-blood AUC ratios ranged from 0.36 (eye lens) to 17.6 (stomach wall). ^{14}C-JNJ-53718678 related radioactivity distributed to pigmented tissues (uveal tract: 12.9; skin 1.0). The lung-to-blood ratio was 1.9.

Following incubation of ^{14}C-JNJ-53718678 in human hepatocytes, metabolites formed via direct *N*-glucuronidation (M8) and via *N*-dealkylation with the loss of the trifluoroethyl moiety (M5) were the most prominent entities. Three different metabolites formed by addition of 1 oxygen were observed (M1, M3, M4), and 3 metabolites formed by addition of 1 oxygen combined with glucuronidation (M7, M9, M10) were also seen. Moreover, *N*-dealkylation at the level of the 5-chloro-2-methyl-indole nitrogen (M12; JNJ-53541683) was observed. All metabolites observed in human hepatocytes were also seen following incubation of ^{14}C-JNJ-53718678 in at least 1 preclinical species. The glucuronide M8 was observed in trace amounts in rabbit and human hepatocytes. In infant human hepatocytes, main metabolites corresponded to those observed in adult human hepatocytes and in vivo in humans with M5 being by far the major metabolite. Following single oral administration of ^{14}C-JNJ-53718678 to adult rats, unchanged JNJ-53718678 was the more important entity in plasma both in males and females. M1 and M12 were the main circulating metabolites. Exposure to M1 and M12 was 2- and 1.4-fold lower than that of unchanged JNJ-53718678 in male rats, respectively, and 10- and 20-fold lower in female rats, respectively. In feces, mainly metabolites were observed. Unchanged JNJ-53718678 represented about 13% and 27% of the administered dose. In minipig plasma, unchanged JNJ-53718678 was the most important entity at early time points with M12 becoming most important later on. In minipig feces, unchanged drug was the most important entity (around 35% of the dose); main route of metabolic clearance was oxidation to M1 (around 11% of the dose). M5 and M3 represented less than 5% of the administered dose. Following single and repeated oral administration of JNJ-53718678 to juvenile rats of different post-natal ages, circulating entities found in the plasma were unchanged JNJ-53718678 and oxidative and dealkylation metabolites. Glucuronidation of M1 was an important metabolite (M7) in the first week of dosing. The ontogeny of the metabolic enzymes in rat does not impact exposure to JNJ-53718678. Plasma levels of M5 (JNJ-54175794), M12 and M19 (JNJ-54564071) have been detected in repeated dose toxicology studies conducted in juvenile and adult dogs and neonatal minipigs.

Cytochrome P450 (CYP)3A4 is the major CYP enzyme involved in JNJ-53718678 phase 1 metabolism in human hepatocytes. Uridine diphosphate (UDP) glucuronyl transferase (UGT) 1A3 and UGT1A4 are involved in the formation of the glucuronide M8. In human liver microsomes, JNJ-53718678 did not show any significant inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 mediated metabolism up to the highest JNJ-53718678 concentration tested (IC_{50} values >15 μM), while it was shown to be a moderate to strong inhibitor of CYP3A4 (IC_{50} 1-2 μM). It was also shown to be an inducer of CYP3A4 (≥1.5 μM) and CYP2B6 (≥5 μM), but not of CYP1A2 (up to 10 μM) in human hepatocytes.

JNJ-53718678 was found to be a substrate, but not an inhibitor, for P-glycoprotein (P-gp; efflux ratio 9.6) and breast cancer resistance protein (BCRP) in vitro. Based on the observed rapid but

passive uptake of JNJ-53718678 by suspended human hepatocytes, in vivo clearance of JNJ-53718678 will likely not be hepatic uptake-limited or sensitive to interactions with hepatic uptake inhibitors. Further evidence was obtained in human hepatocytes in sandwich cultures showing similar metabolites with similar relative abundances present in intracellular and bile canalicular compartments with a low fraction residing in bile canaliculi. In vitro, JNJ-53718678 inhibits organic-anion-transporting polypeptide (OATP)1A2 (IC_{50} 0.6 μM), OATP1B1 (IC_{50} 3.5 μM), organic anion transporter (OAT)3 (IC_{50} 4.2 μM), organic cation transporter (OCT)1 (IC_{50} 3.7 μM), OCT2 (IC_{50} 2.1 μM), but not OAT1 up to 9.6 μM, not OATP1B3 up to 12 μM and not OATP2B1 up to 10 μM. For multidrug and toxin extrusion (MATE)1 the IC_{50} was >8.5 μM and for MATE2-K the IC_{50} was ~ 8.5 μM. JNJ-53718678 is not a substrate for OATP1A2 and OATP2B1 up to 15 μM.

Toxicology

Single JNJ-53718678 doses up to 1,500 mg/kg (maximum feasible dose) in rats, up to 150 mg/kg in dogs and of 50 mg/kg in minipigs were well tolerated. At the highest dose in rats excessive salivation was seen, while in dogs vomiting and excessive salivation were observed at all doses. No signs were present in minipigs.

The main findings after giving rats repeated JNJ-53718678 doses for 5 days of 750 mg/kg/day or for 1 month of 75 and 500 mg/kg/day were rodent-specific adaptive changes (enzyme induction) in liver, thyroid, pituitary gland, and/or adrenal gland, sometimes accompanied by changes in serum parameters such as cholesterol, γ-glutamyltransferase (GGT) and protein levels. In addition, in the 1-month study, dose-related salivation was noted at all doses (25-500 mg/kg/day). Minimal effects considered non-adverse, related to fibrinogen (decrease) and thrombocytes (increase) were present from 75 mg/kg/day onwards, and functional coagulation parameters (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) were prolonged at 500 mg/kg/day, without increased propensity for bleeding. All changes except for some parameters in females dosed at 500 mg/kg/day reverted to normal. The no observed adverse effect level (NOAEL) was set at 75 mg/kg JNJ-53718678 per day. At this dose, mean C_{max} and $AUC_{0\ 24h}$ values for males were 3,240 ng/mL and 11,600 ng.h/mL and for females were 9,240 ng/mL and 52,600 ng.h/mL, respectively.

JNJ-53718678 doses up to 250 mg/kg/day during 2 weeks given to dogs, resulted in dose-related vomiting, decreased food intake and salivation at all doses, leading to body weight (BW) loss from the mid dose (75 mg/kg/day) onwards, and ultimately emaciation in some animals. Small stomach erosions as a consequence of frequent vomiting were noted at the high dose (250 mg/kg/day). At ophthalmic examination, miosis was seen in dogs given 250 mg/kg/day. Several dogs dosed at 250 mg/kg/day showed minor to overt increases in liver enzymes (alanine aminotransferase and aspartate aminotransferase [AST]), which were accompanied by hepatocellular single cell necrosis in 1 dog. Recovery was evident after 1 month, except for food consumption (FC) in females. The NOAEL was set at 25 mg/kg/day. At the NOAEL, the mean C_{max} and AUC values of JNJ-53718678 for males were 4,270 ng/mL and 32,300 ng.h/mL and for females were 3,920 ng/mL and 29,800 ng.h/mL, respectively. Target systems for toxicity are the liver and the gastrointestinal system.

A 2-day repeated dose study was conducted in minipigs at doses of 0, 50, 150, and 300 mg/kg/day. The highest dose was considered above the maximum tolerated dose (MTD) as animals showed continuous BW loss as a result of decreased FC, which was likely related to the ulceration/necrosis of the non-glandular stomach. Other findings at this dose level were extensive vomiting, marked changes in bilirubin which correlated histologically with icterus and cholestasis in the bile ducts and caniculi in 1 animal. In addition, the animals presented increased bilirubin, aspartate aminotransferase (AST) and decreased albumin. Red blood cell (RBC) parameters and platelets were decreased while reticulocytes were increased. Changes in white blood cell subsets and increased globulin were indicative of an acute inflammatory response. Plasma exposures were high and did not decline within 72 hours after the second dose was given. C_{max} increased after the second dose, indicating accumulation after repeated dosing. At this dose the mean C_{max} and $AUC_{0\ 24h}$ values after the second dose were 28,100 ng/mL and 622,000 ng.h/mL, respectively. The animals were sacrificed 1 week after the start of dosing. At the 150-mg/kg/day dose, changes in bilirubin were obvious and short-lasting, BW loss in relation with decreased food consumption (FC) was noted. At this dose, almost all changes were reversible. The 50-mg/kg/day dose was well tolerated with some minor non-adverse changes in clinical pathology. Target organs after dosing twice up to 300 mg/kg/day were the stomach, the intestinal tract, and the hepatobiliary system.

Oral administration of JNJ-53718678 in minipigs for 2 weeks was well tolerated and without mortality up to the highest dose of 25 mg/kg/day. Higher BW gain values and minor hematology and serum chemistry changes were observed, and no target organs were identified after repeated dosing. High, plateau-like exposure and increasing exposure upon repeated dosing (versus single dosing) was seen from the mid dose (ie, 10 mg/kg/day) onwards. After 2 weeks of repeated dosing at 25 mg/kg/day, the mean C_{max} and $AUC_{0\ 24h}$ values were 4,710 ng/mL and 87,200 ng.h/mL, respectively. In minipigs dosed for 28 days at the 25 mg/kg/day in a GLP study, findings were minimal or adaptive in nature in some animals (increased reticulocyte count and hematopoiesis). Other animals dosed at 25 mg/kg showed exposures overlapping with those observed in animals of the high dose group that started at a dose of 50 mg/kg/day and were reduced to 35 mg/kg/day (ie, the 50/35 mg/kg/day dose group). Target organ systems in the 25 and 50/35 mg/kg/day dose groups were primarily circulating white and red blood cells, leading to hemosiderin deposition in the liver and adaptive changes in hematopoietic organs (bone marrow [BM], spleen). The effects on white and red blood cells in animals dosed at 50/35 mg/kg/day after a 28-day dosing-free period showed signs of ongoing recovery, which was not the case for the liver pigment deposition in females. The No Observed Effect Level (NOEL) was 10 mg/kg/day with mean C_{max} and AUC values for male minipigs of 1,510 ng/mL and 21,200 ng.h/mL, and for female minipigs of 1,750 ng/mL and 31,500 ng.h/mL, respectively.

In the first pilot juvenile study in rats, in which pups aged PND1 or PND8 were dosed orally with JNJ-53718678 up to 200 mg/kg/day for a maximum of 3 weeks, no test article-related mortality or clinical signs were noted. A transient effect on BW gain was observed after the first dose on PND1 only, without showing a dose relationship. In a second pilot juvenile study in rats, in which pups aged PND4 were dosed orally with JNJ-53718678 at 300 and 400 mg/kg/day for 7 days, liquid feces, urogenital erythema, and decreased mean BW gains were observed.

In the GLP juvenile study in rats, doses of 50 up to 400 mg/kg/day were given for 4 weeks from PND4 onwards. Excessive salivation (all doses) and a soft distended abdomen were observed, as well as periodically slightly lower BW gain associated with lowered FC from 150 mg/kg/day onwards. Some minor changes were observed in serum parameters (triglycerides [all doses], cholesterol [400 mg/kg/day] and albumin [400 mg/kg/day]). Test item-related histologic findings comprised of centrilobular hepatocellular hypertrophy from 150 mg/kg/day onwards with hepatocellular cytoplasmic vacuolation and thyroid follicular hypertrophy at 400 mg/kg/day. A higher incidence and severity of papillary mineralization was seen in the kidneys in all JNJ-53718678 treated groups. None of the findings described above were considered adverse and all findings were (almost) fully recovered (except triglyceride levels in high dose males) by the end of the recovery period. Therefore, the NOAEL was set at 400 mg/kg/day. Corresponding C_{max} and $AUC_{0\ 24h}$ values on Day 0 (PND4) were 28,800 ng/mL and 259,000 ng.h/mL for males and 23,700 ng/mL and 330,000 ng.h/mL for females, respectively. Corresponding C_{max} and $AUC_{0\ 8h}$ values on Day 24 (PND28) were 26,800 ng/mL and 170,000 ng.h/mL for males and 31,300 ng/mL and 171,000 ng.h/mL for females, respectively.

In the pilot juvenile study in dogs, in which puppies aged PND1 were dosed orally with JNJ-53718678 at 10 up to 75 mg/kg/day during 4 weeks, JNJ-53718678 was well tolerated without adverse effects. No organ weight changes, gross observations or histological changes were observed.

In the pilot juvenile study in minipigs, piglets were dosed orally from PND1 onwards with JNJ-53718678 at 10 up to 75 mg/kg/day for up to 4 weeks. The 75-mg/kg/day dose was administered to 1 animal and considered to be above the MTD, as the animal was sacrificed, after showing a poor clinical condition resulting from vomiting. A relationship with the test article cannot be entirely excluded. Dosing up to 50 mg/kg/day resulted in slightly to overtly lower BW gains (all doses), and low RBC parameters and increased reticulocyte levels with high total bilirubin concentrations (from 25 mg/kg/day onwards) as main findings. In addition, at 50 mg/kg/day slightly increased fibrinogen levels were noted. At 75 mg/kg/day, higher total (direct and indirect) bilirubin levels and a higher urea concentration were measured. An increase in extramedullary hematopoiesis in spleen and liver, as well as starry-sky appearance of the splenic red pulp and BM (from 10 mg/kg/day onwards), lower BM cellularity (at 50 mg/kg/day) and thymic atrophy (from 25 mg/kg/day onwards) were observed at histopathology.

In the GLP juvenile study in minipigs, doses of 5 up to 25 mg/kg/day were administered from PND1 onwards for 5 weeks. A dose of 25 mg/kg/day was not well tolerated, and resulted in gastric ulceration and inflammation, low RBC parameters (RBC count, hemoglobin concentration and packed cell volume) with reticulocyte response and increased (extramedullary) hematopoiesis, increased bilirubin levels (both direct and indirect), decreased fibrinogen levels, and BW loss upon weaning. These findings were (mostly) reversible at the end of the 4-week recovery period. A minimal to slight, non-adverse increase in tingible body macrophages was noted in the BM of females dosed at 10 mg/kg/day. The NOAEL in this study was set at 10 mg/kg/day. Corresponding C_{max} and $AUC_{0\ 24h}$ values (PND35) were 4,870 ng/mL and 77,300 ng.h/mL for males and 4,180 ng/mL and 73,300 ng.h/mL for females, respectively.

JNJ-53718678 did not show any genotoxic potential in a bacterial reverse mutation test, and in in vitro and in vivo micronucleus tests. Furthermore, it is not irritating to the eye, is not skin sensitizing and is not phototoxic in vitro. JNJ-53718678 was classified as moderately cytotoxic in a high content screen assay. JNJ-53718678 did not induce mitochondrial toxicity.

When JNJ-53718678 was spiked with 5% of JNJ-65101335, a potential degradant, the in vitro micronucleus test in TK6 cells was negative. In the 1-month toxicity study in rats, dosing JNJ-53718678 up to 150 mg/kg/day with or without 5% of JNJ-65101335 was well tolerated, and results were similar to previous studies in the rat. No additional toxicity was observed due to JNJ-65101335.

Clinical Studies

Human Pharmacokinetics and Product Metabolism

Single Dose

In the single-dose escalation (SDE) part of Study 53718678RSV1001, mean C_{max} of JNJ-53718678 increased proportionally with dose after administration of JNJ-53718678 doses between 25 mg and 1,000 mg under fasted conditions. Mean AUC from time of administration extrapolated to infinity ($AUC_{0\infty}$) of JNJ-53718678 increased slightly more than dose-proportionally with increasing JNJ-53718678 dose from 25 mg to 1,000 mg. Median time to reach C_{max} (t_{max}) was 1.00 h, except for the 1,000-mg dose group, in which it was 2.50 h. Similar mean apparent terminal elimination half-lives ($t_{1/2term}$) for the different dose groups were observed.

Based upon data from Study 53718678RSV1004 in healthy Japanese adult men and Study 53718678RSV1001, C_{max} and $AUC_{0\infty}$ for JNJ-53718678 are similar between Caucasian and Japanese subjects.

In Study 53718678RSV1009, the effect of JNJ-53718678 on the cardiac repolarization interval in healthy adult subjects was evaluated with dosing up to 4,500 mg. Part 1 of the study was the dose escalation part; based on the PK and safety results of Part 1, the supratherapeutic dose of 4,500 mg was selected for Part 2 of the study, the thorough QT (TQT) part. Exposure-response analysis was performed to determine the relationship between the concentrations of JNJ-53718678 and QT/QTc interval changes extracted from Holter monitor electrocardiogram (ECG) data. Based on this analysis, an important potential risk of QT interval prolongation was identified for JNJ-53718678. The model-predicted mean individual-corrected QT interval (ΔΔQTcI) (90% CI) at the observed geometric mean of the C_{max} of the effect compartment concentration following a single dose of 500 mg (2,165 ng/mL) and 4,500 mg (10,153 ng/mL) JNJ-53718678 was 4.8 ms (4.2; 5.3 ms) and 20.3 ms (18.2; 22.3 ms), respectively. The highest C_{max} at the effect compartment following a single dose associated with an upper limit of the 90% CI for ΔΔQTcI <10 ms was 4,350 ng/mL, which corresponds with approximately a single dose of 1,000 mg in an adult. For more details on the analysis, refer to the IB Addendum.[16] A change to a twice daily (bid) dosing regimen (see Section 6) and several other mitigation measures to safeguard the subjects (see Section 1.2.5) have been implemented.

Multiple Dose

Adult Population

In the multiple-dose escalation (MDE) part of Study 53718678RSV1001 in adult subjects under fed conditions, predose plasma concentrations (C_{trough}) reached steady state after 1 day of treatment with JNJ-53718678. On Day 8, JNJ-53718678 C_{max} and $AUC_{0\ 24h}$ increased dose-proportionally with increasing JNJ-53718678 dose from 250 mg every 24 hours (q24h) to 500 mg q24h. Fluctuation was lower for the 250 mg twice daily (bid) regimen compared with the 500 mg once daily (qd) regimen. The total amount of JNJ-53718678 excreted in urine over the dosing interval at steady state was low, and similar between dose regimens.

In Study 53718678RSV2001 in adult subjects, the PK profile of JNJ-53718678 at multiple doses of 75 mg, 200 mg, and 500 mg qd for 7 days was evaluated in healthy adult subjects inoculated with RSV-A Memphis 37b virus. The PK results from this study were consistent with those from corresponding regimens in Study 53718678RSV1001, indicating that viral infection did not affect the PK of JNJ-53718678.

Interim analysis results from Study 53718678RSV2004 in RSV-infected adult patients demonstrate that the population (pop)PK model provides an adequate description of most of the data, however moderate variability existed with exposures greater than expected (~25%) based on healthy volunteer data. The mean (standard deviation [SD]) Day 7 AUC_{24h} and C_{trough} following administration of 500 mg JNJ-53718678 in this study (N 16) were 38,800 (16,600) ng.hr/mL and 698 (546) ng/mL, respectively, compared to 26,520 (7,520) ng.hr/mL and 334 (197) ng/mL, respectively, observed in Study 53718678RSV2001 (N 17).

Pediatric Population

A popPK model for JNJ-53718678 has been developed using data from Study 53718678RSV1001 in healthy adults and data from Study 53718678RSV1005 in RSV-infected pediatric patients. Using this popPK model, the JNJ-53718678 PK parameters $AUC_{0\ 24h}$, C_{min}, and C_{max} were simulated for Days 1, 3, and 7. At the highest doses of 5, 6, and 9 mg/kg qd for the respective age groups, the predicted $AUC_{0\ 24h}$, C_{min}, and C_{max} values were similar or slightly higher than the corresponding PK parameters observed for 500 mg JNJ-53718678 qd in adults.

Food Interaction

In Study 53718678RSV1001, mean C_{max} of JNJ-53718678 was approximately 35% lower and median t_{max} increased from 1 h to 3.5 h when JNJ-53718678 was administered under fed conditions compared with fasted conditions. Mean $AUC_{0\ \infty}$ of JNJ-53718678 was slightly lower (93%) when JNJ-53718678 was administered under fed conditions compared with fasted conditions. Therefore, JNJ-53718678 can be taken with or without food.

Bioavailability of the JNJ-53718678 oral suspension

The interim PK results from the study part evaluating the oral suspension in Study 53718678RSV1007 indicated similar bioavailability of the oral suspension compared to the oral solution formulation, with a relative bioavailability of 109% (C_{max}) and 104% (AUC). Mean C_{max} of JNJ-53718678 was 35% lower when the oral suspension was administered under fed conditions compared to fasted conditions. The mean fed/fasted ratio was 95% for $AUC_{0\infty}$.

Metabolite Profile

Results from the mass balance-study 53718678RSV1008 demonstrated that JNJ-53718678 was the major metabolite in plasma (44% to 47%), with M12, and M37 being the most abundant metabolites at 17-22% and 9.73% of $AUC_{0\ 96h}$ of total radioactivity (TR), respectively; M19, M5, and glucuronide metabolites (M8 and M9) represented 5%, 4%, and 1% (each), respectively. Most of TR was recovered in feces (71%) and urine (20%), with unchanged drug representing 10% to 16% and 1%, respectively. The most important fecal metabolites were primary oxidative metabolites, and in urine, a multitude of minor metabolites were present. The overall comparison of duodenal fluid and feces profiles demonstrated almost complete conversion of the glucuronides to their aglycon; there was overall a good qualitative and quantitative correlation between both profiles

When the abundance of JNJ-53718678 and its metabolites was determined in plasma of healthy volunteers in Study 53718678RSV1001, similar results were obtained: JNJ-53718678 was the major circulating entity; M12 represented more than 10% of total drug related material (TDRM), and M37 represented 9.79%.

Drug-Drug Interaction

In clinical Study 53718678RSV1002, coadministration of JNJ-53718678 and a drug cocktail consisting of CYP enzyme probe drugs (for CYP3A4, CYP1A2, and CYP2C9) and a non-selective P-gp substrate (fexofenadine) suggested that, after single- and multiple-dose administration, JNJ-53718678 is a weak inhibitor and a weak inducer of CYP3A4. JNJ-53718678 had no clinically significant effect on CYP2C9 and CYP1A2. Single and multiple doses of JNJ-53718678 reduced the plasma exposure of fexofenadine. The observed decrease in exposure of fexofenadine after coadministration of a single dose of JNJ-53718678 is due to the inhibition of OATP1A2, an uptake transporter located in the gut; further reduction of the fexofenadine exposure after repeated dosing of JNJ-53718678, was likely due to induction of P-gP.

In clinical Study 53718678RSV1006, JNJ-53718678 was coadministered with itraconazole (a strong CYP3A4 and P-gP inhibitor) and with rifampicin (an inducer of CYP3A4, UGT, and P-gP, and an inhibitor of OATP). $AUC_{0\infty}$ of JNJ-53718678 increased approximately 3-fold upon coadministration with itraconazole 200 mg qd. After coadministration of JNJ-53718678 with a single dose of rifampicin, no significant change in the total exposure of JNJ-53718678 was observed, suggesting the OATP transporter is not involved in the disposition of JNJ-53718678.

However, repeated administration of rifampicin 600 mg qd decreased the exposure of JNJ-53718678, primarily due to induction of CYP3A4.

Efficacy

Adult Population

In Study 53718678RSV2001 in healthy adult subjects inoculated with RSV-A Memphis 37b virus, mean and median RSV viral load AUC from baseline until discharge were lower for all JNJ-53718678 dosing groups (75 mg qd, 200 mg qd, or 500 mg qd JNJ-53718678 for 7 days) as compared to the placebo group with a large variability observed in each of the JNJ-53718678 dosing groups as well as in the placebo group. No clear dose-response relationship could be observed. This was paralleled with lower clinical symptom scores and mucus production for the JNJ-53718678 dosing groups as compared to the placebo group. Hence, antiviral proof-of-concept for JNJ-53718678 has been established.

Pediatric Population

In Study 53718678RSV1005 in pediatric subjects hospitalized due to RSV-infection, a trend towards an early antiviral effect of JNJ-53718678 was observed, despite a limited data set particularly in the placebo arm. An effect on viral load change from baseline on Days 2 and 3, 1 of to 2 logs difference compared to placebo, was observed, as well as an effect on viral load AUC from baseline through Days 3 and 7 (20 to 25% reduction compared to placebo). The exploration of the effects on the clinical course of RSV infection did not reveal a difference between subjects who had received JNJ-53718678 and those who had received placebo in this limited dataset. No dose-response relationship was observed across the JNJ-53718678 dose levels.

Safety and Tolerability

Adult Population

Based on combined safety data from studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001 in adult healthy volunteers receiving the oral solution, no deaths or other serious adverse events (AEs) were reported; 4 subjects discontinued study treatment due to an AE. Among subjects who received at least 1 dose of JNJ-53718678, 70% experienced an AE as compared to 46.7% of all subjects who received placebo. All but 1 of the treatment-emergent AEs reported during these studies were either Grade 1 or Grade 2 in severity; 1 subject who received placebo was reported with a Grade 3 headache in Study 53718678RSV1001. Adverse events observed more frequently (difference in incidence of ≥5%) in subjects who had received at least 1 dose of JNJ-53718678 compared to subjects who received placebo included diarrhea (20.8% vs 11.1%), dysgeusia (10.8% vs 0.0%), epistaxis (7.5% vs 0.0%), fatigue (6.7% vs 0.0%), abdominal discomfort (5.0% vs 0.0%), and hot flush (5.0% vs 0.0%). In general, none of the reported AEs occurred consistently across different studies and most occurred at a low incidence and low severity. Dysgeusia was frequently reported in Study 53718678RSV1001 in subjects receiving JNJ-53718678 and in none of the subjects of the placebo group and was related to the bitter taste of the oral JNJ-53718678 solution. This

observation led to the initiation of Study 53718678RSV1003 to select an optimized taste of this formulation for future studies. The reported AEs of diarrhea may be explained by the presence of 2-Hydroxypropyl-beta-cyclodextrin (HP-β-CD) as an excipient in the JNJ-53718678 and placebo oral formulation, which has been correlated with increased incidences of diarrhea as the main AE. The observed incidence of epistaxis is consistent with the incidences observed in other RSV challenge studies. Hot flush was only reported in the MDE part of Study 53718678RSV1001 and no dose-related incidence was observed.

The incidences of graded and non-graded laboratory abnormalities were generally low in these studies. All graded laboratory abnormalities were either Grade 1 or Grade 2. Graded and non-graded laboratory abnormalities observed more frequently in subjects who had received at least 1 dose of JNJ-53718678 compared to subjects who received only placebo (difference in incidence of ≥5%) included prothrombin activity above normal (non-graded; 72.2% vs 39.1%), triacylglycerol lipase above normal (non-graded; 19.4% vs 13.0%), increased cholesterol (graded: 15.0% vs 8.9%), and eosinophil/leukocyte ratio below normal (non-graded; 7.5% vs 2.2%). Of note, the incidences of the graded laboratory abnormality of increased PT and aPTT were similar between subjects receiving JNJ-53718678 and those receiving placebo (15.8% vs 17.8% and 8.3% vs 11.1%, respectively).

Changes in heart rate, blood pressure, or respiratory rate were observed in some subjects and were considered generally clinically insignificant. These were either Grade 1 or Grade 2 in severity, except for 1 subject from Study 53718678RSV1001 who received 1,000 mg JNJ-53718678 and in whom a Grade 3 increase in respiratory rate was reported. Considering all of the safety data from clinical studies, a consistently greater incidence of any of the observed abnormalities in vital signs parameters was not apparent in subjects receiving JNJ-53718678 compared to subjects receiving placebo.

No prolongations of the QTcF were reported. Changes in electrocardiographic (ECG) parameters were few and generally considered clinically insignificant.

Safety results from Study 53718678RSV1006 and Study 53718678RSV1008 were generally consistent with those from above mentioned studies.

Overall, during these clinical studies in healthy adults or adult subjects inoculated with RSV, JNJ-53718678 at single doses up to 1,000 mg JNJ-53718678 and multiple doses up to 500 mg JNJ-53718678 once daily and 250 mg JNJ-53718678 twice daily, were generally safe and well tolerated. No relation was noted between the incidences of AEs and laboratory/vital signs/ECG abnormalities and the dose level and/or dose regimen of JNJ-53718678. These studies did not identify any safety signal for JNJ-53718678.

In subjects (n 12) from the study part evaluating the oral suspension in Study 53718678RSV1007, 10 subjects (76.9%) were reported with at least 1 AE. The incidence of AEs was similar between the different treatments: 5 (41.7%) subjects receiving the oral solution and 6 (50%) and 4 (30.8%) subjects receiving the oral suspension under fasted and fed conditions, respectively, were reported with at least 1 AE. All AEs were either Grade 1 or Grade 2 in severity. The most frequently

reported AEs (reported in ≥3 subjects) were diarrhea (3 subjects [25.0%] receiving the JNJ-53718678 oral solution, 1 subject [8.3%] receiving the suspension under fasted conditions, and 1 subject [7.7%] receiving the suspension under fed conditions) and oropharyngeal pain (1 subject [8.3%] receiving the JNJ-53718678 oral solution and 2 subjects [16.7%] receiving the suspension under fasted conditions).

The incidences of graded and non-graded laboratory abnormalities were generally low. All graded laboratory abnormalities were Grade 1 or Grade 2 in severity. Most laboratory abnormalities were considered clinically insignificant. One subject who received the JNJ-53718678 suspension under fasted conditions and 1 other subject who received the JNJ-53718678 suspension under fed conditions had triglyceride plasma concentrations above normal which were reported as AEs of blood triglycerides increased (Grade 1 and Grade 2, respectively), which were both considered by the investigator to be doubtfully related to study drug.

Abnormalities in vital signs and ECG-parameters were observed in few subjects (2 subjects at most) and were considered clinically insignificant. No QTcF prolongation was observed.

Study 53718678RSV1009 evaluated the effect of JNJ-53718678 on the cardiac repolarization interval in healthy adult subjects. Results from the completed Part 1 (dose escalation) of Study 53718678RSV1009 demonstrated that a single dose of JNJ-53718678 was generally safe and well tolerated in these healthy adult subjects. No clinically significant safety findings were identified in any subjects dosed under fasted conditions with JNJ-53718678, including the supratherapeutic dose of 4,500 mg. In addition, there were no cardiac AEs and no clinically significant changes in vital signs, ECGs, or laboratory abnormalities. No deaths, SAEs, AEs of at least Grade 3, or AEs leading to discontinuation of study treatment were observed. Among subjects who received 2,000 mg, 3,000 mg, and 4,500 mg doses of JNJ-53718678, 50.0%, 83.3%, and 83.3%, respectively, experienced at least 1 AE as compared to 55.6% of subjects who received placebo. Diarrhea, nausea, and headache were more frequently observed in subjects who received JNJ-53718678 compared to subjects who received placebo.

Results from Part 2 (TQT part) of Study 53718678RSV1009 demonstrated that JNJ-53718678 was generally safe and well tolerated in healthy adult subjects. No SAEs, AEs of at least Grade 3, or deaths were reported during Part 2 of the study. No clinically significant changes in vital signs or laboratory abnormalities were reported. An AE leading to early study termination was reported for 3 subjects:

- One subject was reported with prolonged QTcF (>450 to ≤480 ms), based on findings from the safety ECG, during JNJ-53718678 (4,500 mg) treatment period, which was considered moderate in severity and probably related to the study agent. The AE resolved the same day.
- One subject was reported with the AEs vomiting, nausea, and headache during the 4,500 mg JNJ-53718678 treatment period. The AEs vomiting and nausea were considered mild in severity and possibly related to the study agent. The AE headache was considered mild in severity and doubtfully related to the study agent. A second event of vomiting was reported on the same day and was considered moderate in severity and possibly related to the study agent. These AEs resolved the same day.

- One subject was reported with a skin reaction during the 400 mg moxifloxacin treatment period. This AE was considered mild in severity and possibly related to the study agent. The AE resolved the same day.

At least 1 AE was reported in 12 (52.2%) subjects after receiving 500 mg JNJ-53718678, 22 (88.0%) subjects after receiving 4,500 mg JNJ-53718678, 9 (39.1%) subjects after receiving placebo, and 12 (50.0%) subjects after receiving 400 mg moxifloxacin. During the treatment phase, diarrhea, nausea, and headache were more frequently observed in subjects who received 4,500 mg of JNJ-53718678 compared to subjects who received 500 mg of JNJ-53718678, placebo, or 400 mg of moxifloxacin.

Based on exposure-response analysis, an important potential risk of QT interval prolongation was identified for JNJ-53718678 (see above). For more details on the analysis, refer to the IB Addendum.[16] A change to a bid dosing regimen (see Section 6) and several other mitigation measures to safeguard the subjects (see Section 1.2.5) have been implemented.

Mean changes in safety ECG parameters were generally minor, and none of them were considered clinically relevant except for 1 event of prolonged QTcF in 1 subject, which was reported as AE and led to study discontinuation (see above). Following moxifloxacin treatment, mean changes in ECG parameters were consistent with the use of moxifloxacin and were not considered clinically relevant.

- Two subjects (4,500 mg JNJ-53718678 and placebo) had an abnormal QTcF value between 450 and 480 ms, leading to early study discontinuation for 1 subject due to AE.
- Six subjects had an abnormal QTcF change from baseline between 30 and 60 ms (2 [8.0%] after receiving 4,500 mg JNJ-53718678, 1 [4.3%] after receiving placebo, and 3 [12.5%] after receiving 400 mg moxifloxacin) but the values remained within normal range. None of the subjects had an abnormal QTcF change from baseline >60 ms.

Interim analysis results (N 67) from Study 53718678RSV2004 demonstrated that JNJ-53718678 was generally safe and well tolerated in RSV-infected non-hospitalized adults. No new safety signal was identified.

There were no deaths, no treatment-emergent SAEs, and no AEs of severity Grade 3 or 4 in Study 53718678RSV2004. Overall, 55.6% of subjects experienced at least 1 treatment-emergent AE (TEAE), of which diarrhea was the most frequently reported TEAE. The overall incidence of TEAEs was smaller in the JNJ-53718678 500 mg group (36.4%) than in the placebo group (59.1%). The highest incidence rate of TEAEs was observed in JNJ-53718678 80 mg group (73.9%). The incidence of TEAEs leading to study medication discontinuation was higher in JNJ-53718678 500 mg group (13.6%) than in JNJ-53718678 80 mg group (8.7%), or the placebo group (4.5%). There were 2 subjects (in JNJ-53718678 500 mg group) with AE (diarrhoea) leading to permanent study discontinuation. ECG abnormalities were infrequently reported. No cardiac safety signal was identified. Graded and non-graded laboratory abnormalities and vital signs observations were generally consistent with those observed in the pooled Phase 1 dataset.

Overall, the oral suspension formulation was generally safe and well tolerated in healthy adult subjects.

Pediatric Population

In Study 53718678RSV1005 in pediatric subjects receiving the oral solution, no deaths, Grade 4 AEs, or AEs leading to study discontinuation or permanent stop of study drug were reported. Four serious adverse event (SAE)s were reported, 2 in the JNJ-53718678 (combined) treatment group (rhinitis and bronchiolitis) and 2 in the placebo group (pneumonia and bronchiolitis). These were reported as serious because of rehospitalization and were considered by the investigator to be not related to the study drug. The majority of subjects were reported with at least 1 AE, at similar incidence rates in both treatment arms (28/37 subjects [75.7%] in the JNJ-53718678 (combined) treatment group vs 6/7 subjects [85.7%] in the placebo group, respectively). Most of the reported AEs were Grade 1 or Grade 2 in severity. Two Grade 3 (severe) AEs were reported (both bronchiolitis; 1 each in the JNJ-53718678 [combined] and placebo group, both were also reported as SAEs). By body system or organ class, most AEs were related to gastrointestinal disorders and infections and infestations in the JNJ-53718678 (combined) and placebo group. By dictionary-derived term, most frequently reported in subjects receiving JNJ-53718678 (reported in ≥10% of subjects) were vomiting, upper respiratory tract infection, and feces soft. Adverse events reported in ≥10% (ie, ≥4 subjects) of subjects receiving JNJ-53718678 that were considered by the investigator to be at least possibly related to study drug were feces soft (18.9%) and vomiting (21.6%).

Laboratory abnormalities were infrequently reported and of low severity (maximal Division of Microbiology and Infectious Diseases [DMID] Grade 2). None were observed more frequently (difference in incidence of ≥5%) in the JNJ-53718678 (combined) group compared to the placebo group. Six AEs related to (non-)graded laboratory abnormalities were reported during the study, of which 2 were considered to be at least possibly related to study drug by the investigator (Grade 2 anemia and Grade 2 leukocytosis).

No clinically relevant differences in incidence rates of vital signs abnormalities were observed between JNJ-53718678 and placebo. One subject (placebo) was reported with the Grade 1 AE of tachycardia considered not related to study drug by the investigator. ECG abnormalities were scarce and generally not considered clinically relevant. One subject (active treatment) was reported during the follow-up phase (1 day after end of treatment) with a Grade 1 AE of QRS axis abnormal considered to be possibly related to study drug by the investigator. No QTcF prolongation was reported.

Interim analysis of Study 53718678RSV2002 confirmed the previously established safety profile of JNJ-53718678. No changes from baseline in QTcF or QT interval corrected for heart rate according to Bazett's formula (QTcB) of >60 ms were reported.

Overall, treatment with JNJ-53718678 was generally safe and well tolerated in pediatric subjects and no safety signals arose in pediatric subjects compared to the previously established safety profile in adults.

1.2. Benefit-risk Evaluations

1.2.1. Known Benefits

JNJ-53718678 at daily doses of 75, 200 and 500 mg given for 7 days has shown an antiviral effect and reduced the signs and symptoms of RSV infection in healthy adults in an RSV human challenge model. Despite a limited data set, in particular the small placebo group, a trend towards an early antiviral effect of JNJ-53718678 was observed for viral load change from baseline and for viral load AUC in the pediatric population based on data from Study 53718678RSV1005 (Section 1.1). However, the clinical benefit of this compound remains to be established.

1.2.2. Potential Benefits

Subjects participating in this study might have a benefit regarding the clinical course of their RSV infection. Treatment with JNJ-53718678 may reduce the severity and duration of RSV signs and symptoms, and their impact on functioning, the effect of RSV infection on physiologic parameters, prevent progression to more severe disease status, reduce the need for and duration of supportive care (eg, oxygen supplementation, IV fluids/feeding, days of hospitalization), and accelerate the subjects' return to pre-RSV health status. The unequal randomization (2:1 active: placebo in each age group) affords the majority of subjects the potential benefit of JNJ-53718678 treatment. Results from the proposed study may be useful in developing a new antiviral therapy for RSV infection.

1.2.3. Known Risks

As a formal adverse drug reaction analysis has not yet been conducted for JNJ-53718678, known risks associated with JNJ-53718678 have not been identified.

1.2.4. Potential Risks

All therapies have the potential to cause adverse experiences.

During completed studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, 53718678RSV1008, and 53718678RSV2001, a total of 190 subjects were enrolled, of which 156 received at least 1 dose of JNJ-53718678 (oral solution) as single doses up to 1,000 mg or multiple doses up to a total daily dose of 500 mg (as 500 mg qd or 250 mg twice daily [bid]) for up to 13 days. Of those, 106 were healthy adult subjects and 50 were healthy adult subjects who were inoculated with RSV-A Memphis 37b virus. In Study 53718678RSV1003, 12 subjects were enrolled but they were only to taste and not to swallow the oral solutions of JNJ-53718678.

In the ongoing Study 53718678RSV1007, several oral concept formulations are being evaluated in separate study parts. In the study part evaluating the oral suspension, 12 subjects received the JNJ-53718678 oral solution and the JNJ-53718678 oral suspension.

During Study 53718678RSV1005, 44 pediatric subjects hospitalized due to RSV-infection were enrolled, of which 37 subjects received JNJ-53718678 (oral solution) and 7 received placebo.

Please refer to Section 1.1 for details on the reported AEs and laboratory/ECG abnormalities in the studies conducted to date.

Based upon the limited clinical data available and considering the early stage of development of JNJ-53718678, no AEs or clinically significant (non-)graded laboratory abnormalities, abnormalities in vital signs parameters, ECG abnormalities, or physical examination findings indicative of a safety concern have been identified.

Based upon the limited available clinical data, no risk related to the hepatobiliary system was identified. However, given the hepatobiliary-related nonclinical findings and because the amount of clinical data is limited, the sponsor considers hepatobiliary effects to be a safety topic of special interest and hepatobiliary function will be monitored by routine hepatobiliary function tests during clinical studies.The evaluation of JNJ-53718678 antiviral activity requires nasal swabbing. However, this is a minimally invasive assessment that at most results in some short-term discomfort for the subject and is usually well tolerated, though occasionally nose bleeding can occur.

Study procedures such as blood sampling carry a potential risk (eg, pain, discomfort, hematoma) to the subject. Therefore, minimal volumes of blood (by venipuncture, heel stick or by finger prick with capillary blood collection) for both safety and PK assessments will be sampled only at carefully selected timepoints. Investigators may use local anesthetics prior to sampling. Other study assessments are not invasive and investigators are encouraged to minimize the stress and discomfort to subjects while performing these assessments.

Study treatment will be provided in addition to, not in replacement of, standard-of-care supportive and symptomatic therapy.

Review of data of the TQT Study 53718678RSV1009 has identified a new important potential risk of QT prolongation for JNJ-53718678 (see Section 1.1 and the IB Addendum[16] for more information). Therefore, a change in dose regimen (see Section 6) and several other measures to safeguard the subjects (see Section 1.2.5) have been implemented.

Overall, the oral suspension formulation used in Part 1 and 2 of the TQT study was generally safe and well tolerated in these healthy adult subjects. Most AEs were mild, with diarrhea being the most frequently reported AE. No Grade 3 or 4 AEs were reported during this study. From a clinical safety perspective, no clinically relevant ECG abnormalities (related to QTcF or other) or cardiovascular AEs were observed in this study. However, exposure-response analysis based on time-matched QTc Holter data demonstrated that, following a single dose of 500 mg, the effect of JNJ-53718678 on cardiac repolarization is not of regulatory concern, but at doses ≥1,000 mg an increase of placebo-corrected change from baseline for the ΔΔQTcI above the threshold of 10 ms can be expected (Section 1.1).

Available clinical safety data do not indicate any safety signal or concern with regards to the cardiovascular system (Section 1.1).

1.2.5. Overall Benefits/Risks

Currently the only available treatment for RSV is supportive care for infants and children requiring hospitalization. Based on the available data and proposed safety measures, the overall risk/benefit assessment for this study is acceptable for the following reasons:

- Antiviral effect proof of concept was established in adult healthy volunteers challenged with a laboratory strain of RSV (Study 53718678RSV2001) as well as in naturally RSV infected pediatric subjects (Study 53718678RSV1005) (Section 1.1);
- The completed studies to date identified no safety concerns and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to JNJ-53718678 by the investigator (Section 1.1);
- No safety concerns were identified in the interim analysis of Study 53718678RSV2004 in non-hospitalized adult participants infected with RSV (Section 1.1);
- Available final data from the ongoing 53718678RSV1005 study in naturally RSV-infected pediatric subjects >1 month to ≤24 months of age and from an interim analysis of Study 53718678RSV2002 in children ≥28 days and ≤3 years of age did not indicate safety concerns (Section 1.1);
- Several safety measures have been proposed to minimize potential risk to subjects, including:

  Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of the subjects in the study.

  Utilization of study treatment discontinuation criteria and stopping criteria (see Sections 10.2 and 10.3).

  Subjects in Cohort 1 are to be hospitalized before treatment initiation allowing for intensive monitoring of subjects at the beginning of the study, until discharge. After discharge from the hospital, for the remainder of the study period, a close follow-up (see Section 9.1.4) is planned with the same visit schedule as Cohort 2 outpatient subjects (study visits on Day 3, Day 5, Day 8, Day 14, Day 21, and a telephone visit on Day 28, when the subject completes the study).

  Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development and safety topic of special interest of JNJ-53718678 as part of the study assessments.

  Safety surveillance will be performed in a manner that minimizes the total number of required invasive procedures (eg, blood draws) to minimize discomfort to study subjects.

  Utilization of result from diagnostic testing (swab) performed as part of standard of care.

  The establishment of an IDMC to monitor data on a regular basis to ensure continuing safety of the subjects enrolled in this study.

  Customary measures taken by investigational staff to ensure that study-specific assessments such as blood sampling and nasal swabbing are performed with as little

additional stress as possible for the children and allowance of the use of local anesthetics prior to blood sampling.

- In view of the identified important potential risk of QT interval prolongation (see Section 1.1, TQT Study 53718678RSV1009), the following measures have been implemented to minimize the potential risk to subjects:

  The selection of the bid dose regimens which, relative to the respective qd dose regimens for which no safety concern was identified, will minimize C_{max} while still maintaining AUC and increasing C_{trough} (see Section 6).

  Specific cardiovascular and ECG-based criteria were established for eligibility assessment (see Section 4.2).

  Close monitoring of the use of concomitant medications will be conducted regularly. Drugs that are moderate or strong CYP3A4 inhibitors and breast cancer resistance protein (BCRP) inhibitors will be disallowed (see Section 8).

  Regular ECG monitoring will be performed at screening and several timepoints during the study, including an ECG around t_{max} on Day 1 and Day 3 (steady state).

  Evaluation of clinical status, AEs, vital signs, physical examination as well as laboratory abnormalities will be conducted as per the TIME AND EVENTS SCHEDULE. Additional unscheduled visits/assessments may be performed based on the overall clinical picture as per the investigator's clinical discretion.

  Utilization of study intervention discontinuation and withdrawal criteria specific to QT interval changes (see Section 10.3).

  Close monitoring of hypokalemia and hypomagnesemia and corrective actions in case of laboratory abnormalities for these analytes during the treatment period (see Section 9.3).

  QT prolonging drugs will be disallowed during the treatment period (see Section 8).

  Specific toxicity management for cardiac and ECG related events was established (see Section 9.3.1).

1.3. Overall Rationale for the Study

This study will explore the antiviral activity, clinical outcomes, safety, tolerability, and PK/PD relationships of high and low doses of JNJ-53718678 in children ≥28 days and ≤3 years of age with acute respiratory tract infection due to RSV, in 2 cohorts ie, hospitalized (Cohort 1) and outpatients (Cohort 2). The results of this study will enable selection of the dose and clinical endpoints for subsequent Phase 3 studies.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

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.

Secondary Objectives

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

Exploratory Objectives

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)

2.1.2. Endpoints

Primary Endpoint

The primary efficacy endpoint is the RSV viral load area under the curve (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

The secondary endpoints are:

- 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 (ie, 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)

- 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 (see Section 3.1), the same parameters as assessed by the biosensor will be recorded from the standard-of-care monitoring/assessments as part of the substudy assessments (refer to the substudy Clinical Protocol for detailed information).
- body temperature as measured by the parent(s)/caregiver(s) and recorded in the temperature log (Attachment 8) on the electronic device
- need for (re)hospitalization during treatment and follow-up

in hospitalized subjects only:

- 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 (ie, without requirement of supplemental oxygen compared with pre-RSV infection status)
- time to discharge (from initial admission and from initiation of treatment)
- time to clinical stability, with clinical stability evaluated by the investigator (from initial admission and from initiation of treatment)
- 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 (eg, not transferred to ICU due to bed availability)
  - requiring ICU level of care is defined by some specific conditions:
    - acute or imminent respiratory failure
    - treatment of complicated acid-base or electrolyte imbalances
    - cardiogenic shock
    - acute congestive heart failure
    - hemodynamic instability
  - having other conditions requiring specialized equipment and/or staff competencies only available in the ICU
- 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 noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, 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

Exploratory endpoints include:

- the occurrence of complications with onset after treatment initiation that are associated with RSV per investigator assessment:

  bacterial superinfections (eg, pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment)

  otitis media, bronchiolitis, viral pneumonia

  exacerbations of underlying pulmonary disease (eg, 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 (eg, nasopharyngeal and/or tracheal aspirate samples)
- virologic parameters derived from the RSV viral load as measured by quantitative viral culture

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV (ie, a decrease in RSV viral load 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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study 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 [Cohort2]).

Subjects with at least mild RSV disease will be enrolled (ie, at least one symptom of upper respiratory tract infection, at least one symptom of lower respiratory tract infection, and at least one systemic/general symptom; see Section 4.1). Eligible subjects can be otherwise healthy or have (a) risk factor(s) for severe RSV disease (eg, prematurity at birth [only for subjects ≥3 months of age at the time of consent] or having a comorbid condition eg, bronchopulmonary dysplasia, congenital heart disease, other congenital diseases, Down syndrome, neuromuscular impairment,

cystic fibrosis, or recurrent wheezing/asthma) (see Table 1). Subjects who are immunocompromised are excluded.

Table 1: Risk Factors for Severe RSV Disease

Prematurity at birth[a]
Bronchopulmonary dysplasia
Congenital heart disease
Down syndrome
Neuromuscular impairment
Cystic fibrosis
Recurrent wheezing[b]
Asthma
Other congenital disease

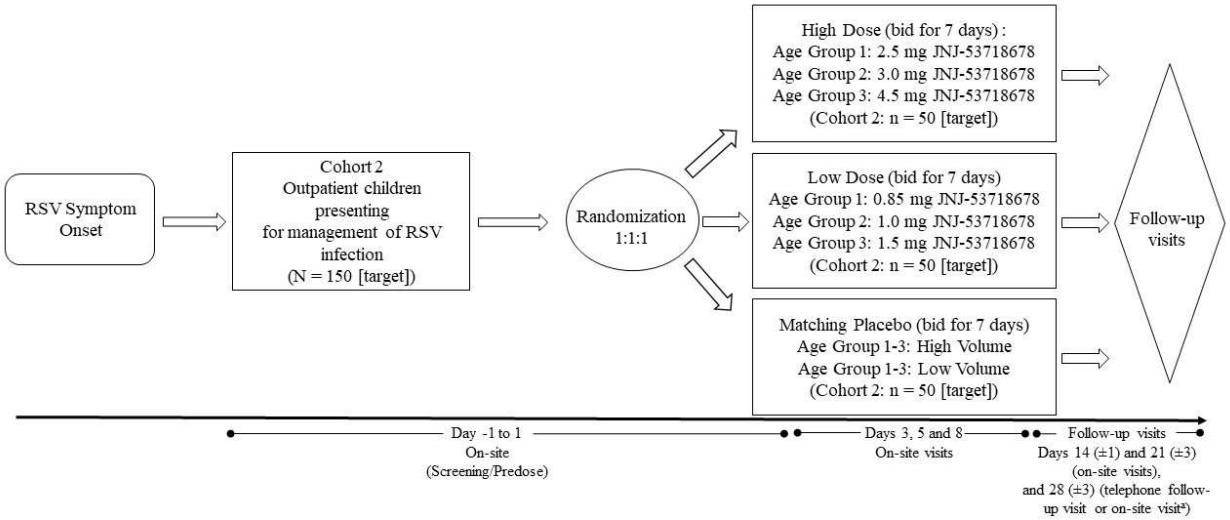
[a] Only for subject ≥ 3 months of age at the time of consent
[b] Recurrent wheezing is defined as ≥3 episodes of wheezing dyspnea since birth

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 interim analysis (see Section 11.1.3).

Study participants will be identified when they are hospitalized or expected to be hospitalized within 24 hours after presentation to the hospital (Cohort 1) or present for medical care as outpatients (Cohort 2) with symptoms of an acute respiratory illness supporting a diagnosis of RSV infection (eg, nasal congestion, rhinorrhea, pharyngitis, increased respiratory effort, abnormal breathing sounds [wheezing, rales, or rhonchi], cyanosis, cough, apnea, fever, feeding difficulties, dehydration). For newly enrolled subjects in Cohort 2 after Protocol Amendment 6, cough or wheezing should be accompanied by at least one additional LRTI sign/symptom in order to be eligible. 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 (see Section 9.4.1). 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.

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] In case of ongoing adverse event(s)
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

Note: Prior to Protocol Amendment 4, the total daily dose was the same but the daily dosing frequency was qd instead of bid.

Screening must be completed as soon as possible. During screening, a study-specific screening sample (mid-turbinate swab) will be collected for the local diagnosis of RSV infection using a preferably rapid polymerase chain reaction (PCR)- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main study ICF or with the diagnostic ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.

A separate mid-turbinate swab will be collected immediately prior to the first dose for central laboratory analyses to confirm RSV infection (and subtype), to determine the RSV viral load, to perform viral sequencing, and to determine the presence of other viral or bacterial pathogens. If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL each).

Initially, only hospitalized subjects will be recruited (Cohort 1). After the first interim analyses, 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 (see below).

Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first. 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). 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 as defined above) (see Table 1). Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects could be enrolled in the >3 days to ≤5 days stratum). To guarantee the required balance between strata for the interim analyses, enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to an interim analysis and stopped prior to final analysis (see below). Stratum caps and closures are managed separately for each cohort and consider the sample size of the respective cohort for the interim analysis and the total sample size of each cohort for the final analysis.

Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. JNJ-53718678/placebo can be administered with/without food. The study drug will be administered orally using a dosing syringe. For Cohort 1 and during hospitalization, the study drug can also be administered through a nasogastric tube, if already in place. In this document, both administration methods are referred to as “oral dosing”, unless specified otherwise.

Note: Prior to Protocol Amendment 4, the total daily dose was the same but the daily dosing frequency was qd instead of bid.

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).

Study drug will be administered twice daily for 7 days (14 consecutive doses). Doses are based on weight and age group:

- High Dose (Cohort 1: n 48 [target]; 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 1: n 48 [target]; 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 1: n 48 [target]; Cohort 2: n 50 [target]): those randomized to a placebo regimen will be subsequently 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)

Note: The above-mentioned doses refer to the amount of JNJ-53718678-AAA (free form). 20 mg JNJ-53718678-AAA corresponds to 23 of mg JNJ-53718678-ZCL (hemi-tartrate salt of JNJ-53718678-AAA) used in the oral suspension.

In Cohort 1, the study drug will be administered by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel during hospitalization. In case the subject is discharged prior to Day 7, the study drug will continue to be administered at home by the parent(s)/caregiver(s) through Day 7. In Cohort 2, the first dose of study drug will be administered, by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel, at the study site; the study drug will continue to be administered at home by the parent(s)/caregiver(s) through Day 7 or the morning (AM) of Day 8 if the first dose was given PM on Day 1. All subjects will receive standard supportive care for RSV infection as per local SOC considering the restrictions provided in Section 8. All SOC treatment should be recorded as concomitant medication/treatment.

In Cohort 1, subjects can be discharged as of Day 2 if deemed appropriate by the investigator and after completion of the required investigator-performed assessments for that day (except for the evening assessment in case the assessment is to be performed twice daily [bid]). Discharged subjects (Cohort 1) will be required to attend the scheduled study visits as outpatients with the same visit schedule as Cohort 2 subjects, from time of discharge onward. Cohort 2 subjects will have study visits on Day 3, Day 5, Day 8, Day 14, and on Day 21. All scheduled study visits can

also be done as home visits, if feasible for the study site and if allowed per local regulations. On Day 28 (±3), subject's parent(s)/caregiver(s) will be contacted by the site staff for a telephone follow up visit, after which the subject completes the study. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 Follow-Up Visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit for the subject at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28.

In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit (see TIME AND EVENTS SCHEDULE). At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

As an evaluation of antiviral activity, the RSV viral load in nasal secretions will be measured at the central lab using a qRT-PCR assay on mid-turbinate nasal swab specimens, which will be collected at several timepoints during the study as indicated in the TIME AND EVENTS SCHEDULE (see Section 9.2.1). If feasible, the RSV infectious virus load may also be assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples.

Viral resistance will be monitored by sequencing of the F-gene in all baseline samples, and on subsequent samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at discretion of the sponsor's virologist. Sequencing data will not be reported to the investigators (see Section 9.2.3). Sequencing results may be presented in a separate report.

Clinical course and severity of RSV infection will be assessed through different measures (see Section 9.2.2). No well-validated clinical measures are currently available to systematically evaluate severity of RSV disease in pediatric subjects treated in hospitals or community settings. The sponsor developed the Pediatric RSV Electronic Severity and Outcomes Rating Scales (PRESORS) to monitor signs of RSV disease severity observed and rated by clinicians treating pediatric subjects (clinician PRESORS: Attachment 4) as well as by the subject's parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS: Attachment 5). Parent(s)/caregiver(s) and clinicians use an electronic device to record and rate problems breathing, coughing, wheezing, feeding, and other signs of RSV disease observed in the subject.

Safety and tolerability, including AEs, laboratory assessments, electrocardiograms (ECGs), vital signs, and physical examination will be assessed throughout the study from signing of the ICF until the subject's last study-related activity (see Section 9.3).

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model (see Section 9.4). 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 (see Table 4). 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 (see Table 4). 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 at this site. For the subjects recruited to Cohort 2 after Protocol Amendment 4, PK samples will be collected approximately one hour after administration of study drug (after the ECGs are obtained if applicable) at Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5 (see Section 9.4.1).

Medical resource utilization (see Section 9.6) and acceptability and palatability of the study drug (see Section 9.7 and Attachment 9) will be assessed.

Leftover mid-turbinate nasal swab and blood samples collected for other testing may be used for exploratory biomarker analyses to determine the effects of JNJ-53718678 on markers of RSV disease, at discretion of the sponsor (see Section 9.8).

See Attachment 10 for guidance on study conduct during the COVID-19 pandemic.

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 to the Sponsor Committee to ensure the safety of enrolled subjects. The IDMC can recommend to the Sponsor Committee to halt a dose arm due to safety concerns. The IDMC will also review safety and PK data from 6 subjects in the subcohort of Cohort 1 and the data of the interim analyses and provide recommendations to the Sponsor Committee. The Sponsor Committee will take a decision considering the IDMC's recommendation. Refer to Section 11.12 for details.

The study will start with Cohort 1 (including the subcohort). The first interim analysis encompassing safety and tolerability, PK, and antiviral effect is planned when at least 36 subjects from Cohort 1 have completed the Day 14 assessments (or discontinued earlier). Enrollment in Cohort 1 will continue during the interim analysis. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 1 (at N 36 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 1 has been randomized. 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.

A second interim analysis is planned, 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) have completed the Day 14 assessments (or discontinued earlier). Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 2 (at N approximately 70-80 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 2 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity and one clinical endpoint (ie, time to resolution of symptoms, considering data of both cohorts), 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, other clinical course and safety-related endpoints will be analyzed. The Sponsor Committee will take a decision considering the IDMC's recommendation. Depending on enrollment status of Cohort 2, the second interim analysis will not be performed, if it is later than or too close to the predicted timing of the planned third interim analysis.

A third interim analysis is planned, preferably at the end of a hemispheric RSV season, when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier) and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 3 (at N approximately 70-80 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 3 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity (data from both cohorts combined) and clinical endpoints (Cohort 2 data only), as well as a sample-size re-estimation for clinical endpoints (Cohort 2 data only). Both the study team and the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account. The maximum number of subjects in Cohort 2 in the study will not exceed 300.

If the study is extended beyond the initially planned sample size in Cohort 2 for the primary analysis (N 150), a fourth interim analysis will be performed preferably at the end of a hemispheric RSV season, after approximately 150 subjects in Cohort 2 have completed the Day 14 assessments (or discontinued earlier), and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 4 (at N approximately 150 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 4 has been randomized. The primary analysis on antiviral activity will be performed during this fourth interim analysis 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 preparations, including regulatory interactions. In addition, the futility and population enrichment analysis will be repeated at this interim analysis. Both the study team and

the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account.

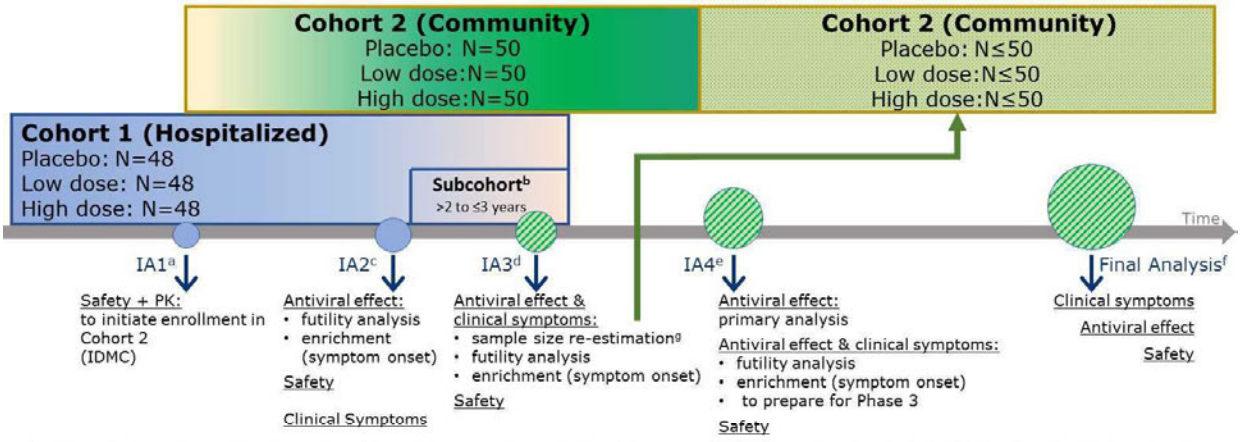
Enrollment will continue during each of the interim analyses.

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 will coincide with the primary analysis. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be stopped once the maximum number of subjects are enrolled in this stratum in both cohorts. Since the number of subjects enrolled in Cohort 2 is the trigger to perform interim analysis 3 and interim analysis 4, enrollment in Cohort 1 in the >3 days to ≤5 days since symptom onset stratum might be stopped, at any time after interim analysis 2, once the maximum number of subjects in this stratum are enrolled for the final analysis. See Section 11.4 for more information. More details on (un)blinding can be found in Section 11.1.

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.

An overview of the different planned analyses is shown in Figure 2.

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.

Additional interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities.

A separate substudy may be performed at selected study sites to explore the feasibility of the use of biosensors for the evaluation of cardio-respiratory parameters (eg, respiratory rate, heart rate, and SpO_2). Details, including objectives and study design, will be described in a separate substudy protocol.

3.2. Study Design Rationale

This Phase 2 multicenter, double-blind, placebo-controlled, randomized study is designed to explore the antiviral activity, clinical outcomes, safety, tolerability, and PK/PD relationships of high and low doses of JNJ-53718678 twice daily for 7 days in children ≥28 days and ≤3 years of age with acute respiratory tract infection due to RSV, in 2 cohorts ie, hospitalized (Cohort 1) and outpatients (Cohort 2). The results of this study will enable selection of the dose and clinical endpoints for subsequent Phase 3 studies.

Blinding, Control, Study Phase/Periods, Intervention Groups

There is currently no approved treatment routinely used for the treatment of RSV infection. A placebo control will be used to establish the frequency and magnitude of changes in virologic and clinical endpoints that may occur in the absence of active treatment. The use of a placebo

control will allow for any AEs or laboratory abnormalities observed during the course of the study to be evaluated properly, ie, to differentiate between events potentially related to the use of JNJ-53718678 vs those related to the underlying disease.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

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 (see Section 6). For dosing purposes, 3 age groups (≥28 days and <3 months; ≥3 months and <6 months or ≥6 months and ≤3 years of age) are defined depending on the subject's age at the time of consent, taking into account the abundancy of specific enzymes (and their maturation) involved in the metabolism of JNJ-53718678 in these different age groups (see also Study 53718678RSV1005).

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 as defined above). Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects could be enrolled in the >3 days to ≤5 days stratum). To guarantee the required balance between strata for the interim analyses, enrollment in the >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. Stratum caps and closures are managed separately for each cohort and consider the sample size of the respective cohort for the interim analysis and the total sample size of each cohort for the final analysis.

Presence or absence of (a) risk factor(s) for severe RSV disease is included as stratification factor due to potentially different (more severe) disease course of RSV infections in subjects with these conditions.

Duration of symptoms onset is included as stratification factor because it is anticipated that there will be a larger treatment effect in subjects with onset of symptoms ≤3 days. In order to analyze the impact of the time since onset of RSV symptoms on the treatment effect, the number of subjects enrolled with time since onset of RSV symptoms of >3 days to ≤5 days will be limited to a maximum of 55% at the time of all planned interim or final analyses.

Population

Subjects in the age group ≥28 days to ≤3 years are targeted, as they are mostly affected by (severe) RSV disease. Both hospitalized (Cohort 1) and outpatient (Cohort 2) subjects are targeted as RSV is a major cause of acute LRTI, resulting into either hospitalization or outpatient medical care. The number of subjects exposed as part of the study has been limited to a minimum to reach the

objectives of the study. A sample size re-estimation based on clinical course endpoints will be performed and may results in an extension of Cohort 2.

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 (see Section 9.4.1). 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.

Dose Selection

The active regimens (high or low dose, adapted to the age groups, see Section 6) evaluated in this design are selected to provide a range of plasma concentrations of JNJ-53718678 to obtain information on antiviral activity, clinical outcomes, safety, tolerability, and PK/PD relationships in the target population of subjects, in the age range of ≥28 days to ≤3 years, infected with RSV.

The high doses (5, 6, and 9 mg/kg, dependent on the age groups) were initially selected based on the results of the PK analysis performed during Study 53718678RSV1005. Pharmacokinetic analysis demonstrated that these doses resulted in observed minimum plasma concentration (C_{min}) and maximum plasma concentration (C_{max}) values within the range of the target concentrations (ie, the exposure observed in adults treated with 500 mg JNJ-53718678 once daily), although associated with slightly higher observed AUC values. Furthermore, based on the safety data from Study 53718678RSV1005, these doses were generally safe and well tolerated and resulted in antiviral effect (see also Section 1.1).

Based on the exposure-response analysis conducted in the TQT Study 53718678RSV1009 in healthy adult subjects, an exposure (C_{max}) related important potential risk of QT interval prolongation was identified. While no safety signal was observed regarding QT prolongation, other ECG abnormalities, or cardiovascular side effects, additional modelling to evaluate alternative dose and dosing regimens, which would allow to maintain the exposures (C_{trough}) at effective levels while reducing the C_{max}, to mitigate this potential risk were performed.

Based on final PK and QTc modeling, a 7-day bid dosing regimen of 2.5, 3, and 4.5 mg/kg for the 3 different age groups (≥28 days to <3 months, ≥3 to <6 months, and ≥6 to <36 months of age, respectively) was selected with disallowance of comedication with moderate or strong CYP3A4 inhibitors. Based on Table 2, the upper limit of the 90% confidence interval for ΔΔQTcI for the bid regimen for each of the age groups remains below 10 ms. It is anticipated that the proposed bid dosing will be in the therapeutic range of JNJ-53718678 for the pediatric population (C_{trough} at least 7 times the protein adjusted at 90% maximal effective concentration), ensuring the highest potential antiviral effect while minimizing the risk of development of resistance, as well as mitigating the important potential risk of QT interval prolongation.

Table 2: Predicted Geometric Mean AUC_{24h}, C_{max}, C_{trough} and ΔΔQTcI Per Age Group After Day 1 and Day 7

Age Group (Dose mg/kg bid)	1 - <3 Months (2.5 mg/kg bid)	3 - <6 Months (3 mg/kg bid)	≥6 - ≤36 Months (4.5 mg/kg bid)
AUC_{24h} Day 1 (ng.hr/mL)	16,500	17,200	17,400
AUC_{24h} Day 7 (ng.hr/mL)	32,900	28,800	21,600
C_{max} Day 1 (ng/ml)	1,220	1,350	1,690
C_{max} Day 7 (ng/ml)	1,870	1,800	1,840
C_{trough} Day 1 (ng/mL)	566	509	292
C_{trough} Day 7 (ng/mL)	998	773	350
ΔΔQTcI Day 1 (ms) (90%CI)	1.95 (0.97-3.66)	2.09 (1.08-3.98)	2.37 (1.19-4.62)
ΔΔQTcI Day 7 (ms) (90%CI)	3.17 (1.34-6.81)	2.92 (1.31-6.23)	2.64 (1.25-5.54)

ΔΔ = placebo-adjusted change from baseline; AUC = area under the plasma concentration-time curve; AUC_{24h} = AUC from administration to 24 hours; bid = twice daily; C_{max} = maximum plasma concentration; C_{trough} = predose plasma concentration; QTcI = individual-corrected QT interval.

The low doses represent one-third of the high dose administered for each age group. These low doses will result in a mean exposure sufficiently low to clearly differentiate from the mean exposure obtained with the high doses, which is required to evaluate the JNJ-53718678 exposure-response relationship for antiviral activity. In Study 53718678RSV1005, the exposures resulting from these doses also demonstrated antiviral effect.

Study Duration

The total study duration for each subject will be approximately 29 days (Screening included). Dosing will last for 7 days (14 consecutive doses) as it has been shown that the duration of viral shedding upon RSV infection is at least that long.[6] Healthy adult volunteers in the challenge study (Study 53718678RSV2001) and hospitalized pediatric subjects in Study 53718678RSV1005 were dosed for 7 days and JNJ-53718678 was generally safe and well tolerated (see Section 1.1).

Clinical Outcomes of RSV Treatment

Treatment with JNJ-53718678 may reduce the severity and duration of RSV signs and symptoms, and their impact on functioning, the effect of RSV infection on physiologic parameters, prevent progression to more severe disease status, reduce the need for and duration of supportive care (eg, oxygen supplementation, IV fluids/feeding, days of hospitalization), and accelerate the subjects' return to pre-RSV health status. The study will compare treatment regimens to evaluate the impact of treatment with JNJ-53718678 on the clinical course of RSV disease.

Biomarker Collection

Leftover mid-turbinate nasal swab and blood samples collected for other testing may be used for exploratory biomarker analyses (eg, proteins including cytokines, microbiome), on the premise that these markers may play a role in the treatment response, safety of JNJ-53718678, or RSV-related disease.

Analyses of biomarkers may be performed at the sponsor's discretion and reported separately from this study.

No human deoxyribonucleic acid (DNA) analyses will be performed on these samples.

Medical Resource Utilization

Treatment of RSV disease with JNJ-53718678 versus placebo may result in lower utilization of hospital or outpatient healthcare services; therefore, comparison will be done between intervention groups.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible after initial presentation at the hospital (Cohort 1) or after presentation for medical care as outpatients (Cohort 2) such that subjects are randomized within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.3, Sample Size Determination.

4.1. Inclusion Criteria

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

1. The subject is a boy or girl ≥28 days and ≤3 years at the time of consent.

2. Each subject's legally acceptable representative (ie, parent(s)/legal guardian) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study, is willing for their child to participate in the study, is willing for their child to remain in the hospital until at least Day 2 (even if not clinically indicated; Cohort 1 only), and is willing/able to adhere to the lifestyle restrictions specified in the protocol (see Section 4.3) and study procedures and assessments to be performed by the parent(s)/caregiver(s) as well as those by the investigator/site staff.
   Note: Prior to signing the main consent form for the study, subject's legally acceptable representative may specifically allow for the collection and testing of nasal mid-turbinate swab by signing the pre-screening (diagnostic) ICF. This is not required if a positive RSV diagnostic result based on a local SOC sample collected within 48 hours prior to anticipated randomization is available and used for determining study eligibility.

3. The subject has been diagnosed with RSV infection using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred) or a rapid-antigen-detection assay.
   Note: If a subject had a positive similar RSV diagnostic test from another study for which (s)he was otherwise ineligible or a SOC test within 24 hours prior to start of screening and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility. Randomization should occur within 24 hours after

start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first.
Note: If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main study ICF or with the diagnostic ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.

4. Criterion modified per Amendment 6:

4.1 The subject has an acute respiratory illness with at least 1 of the signs/symptoms listed in each of the following categories within 24 hours prior to start of screening and at screening, as evaluated by the investigator:

- URTI: nasal congestion, rhinorrhea, pharyngitis, or otitis media; AND
- LRTI: increased respiratory effort (as evidenced by subcostal, intercostal or tracheosternal retractions, grunting, head bobbing, nasal flaring or tachypnea), abnormal breathing sounds (wheezing, rales or rhonchi), cyanosis, apnea, or cough (cough or wheezing should be accompanied by at least one additional LRTI sign/symptom in order to be eligible); AND
- Systemic/general: feeding difficulties, defined as <75% intake of normal food amounts; dehydration; fever; disturbed sleep or disturbed activity level (irritable/restless/agitated/less responsive).

5. The time of onset of RSV symptoms to the anticipated time of randomization must be ≤5 days. Onset of symptoms is defined as the time of the day (or part of the day if time of the day cannot be specified) the parent(s)/caregiver(s) became(s) aware of the first sign and/or symptom consistent with respiratory or systemic/general manifestation of symptoms of RSV infection. The time of symptom onset has to be assessed as accurately as possible.
Note: Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects could be enrolled in the >3 days to ≤5 days stratum).

6. Except for the RSV-related illness, the subject must be medically stable based on physical examination, medical history, and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying condition (RSV disease and/or present risk factor[s] for severe RSV disease) in the study population as evaluated by the investigator. This determination must be recorded in the subject's source documents and initialed by the investigator.

7. The subject must have been assessed per local public health practice and considered not to have SARS-CoV-2 infection during this respiratory infection.

4.2. Exclusion Criteria

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

1. The subject is <3 months postnatal age at screening and was born prematurely (ie, <37 weeks and 0 days of gestation).

2. The subject weighs <2.4 kg or >16.8 kg.

3. The subject had major surgery within the 28 days prior to randomization or planned major surgery through the course of the study.

4. The subject has major congenital anomalies or known cytogenetic or metabolic disorders other than the ones allowed above (see inclusion criterion 6).
Note: Isolated open ductus arteriosus and open foramen ovale are not exclusionary as these are not considered major anomalies. Subjects with congenital heart disease, cystic fibrosis, congenital diaphragmatic hernia, or Down Syndrome are allowed to participate.

5. The subject is considered by the investigator to be immunocompromised within the past 12 months, whether due to underlying medical condition (eg, malignancy or genetic disorder other than immunoglobulin A deficiency, or known HIV infection) or medical therapy (eg, immunomodulators other than corticosteroids for the treatment of comorbidities, chemotherapy, radiation, stem cell or solid organ transplant).

6. The subject has known or clinically suspected hepatitis B or C infection, either acute or chronic active.

7. The subject has known allergies, hypersensitivity, or intolerance to JNJ-53718678 or to any of the excipients of the JNJ-53718678 or placebo formulation (refer to the IB).[17]

8. The subject is currently participating or planned to participate in another clinical interventional study, during their participation in this study.

9. The subject is unwilling to undergo or the parent(s)/caregiver(s) is/are unwilling to have the subject undergoing mid-turbinate nasal swab procedures.

10. The subject has any physical abnormality which limits the ability to collect regular nasal specimens.

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

12. The subject is being treated with extracorporeal membrane oxygenation (Cohort 1 only).

13. The subject is receiving chronic home oxygen therapy at screening.

14. Criterion modified per Amendment 4:

14.1 The subject has other clinically significant abnormal ECG findings not consistent with the present risk factor for severe RSV disease (if applicable) in the study population, as judged by the investigator based on the machine read ECG results at screening.

15. Criterion modified per Amendment 4:

15.1 The subject has a QTcF interval >450 ms per the machine read (mean of triplicate) parameter result confirmed by repeat triplicate ECG recording during screening.

16. The subject is using any disallowed medication as listed in Section 8.

17. Criterion modified per Amendment 4:

17.1 The subject's mother received an investigational RSV vaccination during the pregnancy for this child whose age is <3 months at time of screening.

18. The subject has evidence of one of the following ECG abnormalities per the machine read ECG result confirmed by repeat ECG recording at screening:

- Repetitive premature ventricular contractions (>10/min)
- Second- or third-degree heart block
- Complete or incomplete left bundle branch block or complete right bundle branch block

19. The subject has a personal or first- or second-degree family history of long QT syndrome or sudden cardiac death.

20. The subject has had ANY of:

a) Confirmed SARS-CoV-2 infection (test positive) during the four weeks prior to randomization, OR

b) Close contact with a person with COVID-19 (test confirmed or suspected SARS-CoV-2 infection) within 14 days prior to randomization.

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

the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Lifestyle Restrictions

Parent(s)/caregiver(s) must be willing and able to adhere to the prohibitions and restrictions with regards to the concomitant therapy (see Section 8) during the course of the study for the subject to be eligible for participation.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. 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 (see Table 4). 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 (see Table 4). 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 at this site. In Cohort 2, PK samples will be collected as indicated in the TIME AND EVENTS SCHEDULE.

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, Table 1). Stratification will be applied to each cohort separately, with exception of the subcohort. Subjects with symptom onset ≤3 days before randomization must account for a minimum of 45% % of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of all subjects can be enrolled in the >3 days to ≤5 days stratum). To guarantee the required balance between strata for the interim analyses, enrollment in the >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 (see Section 11.1). Stratum caps and closures are managed separately for each cohort and consider the sample size of the respective cohort for the interim analysis and the total sample size of each cohort for the final analysis. Enrollment in the >3 days to ≤5 days since symptom onset stratum

will be reopened once the last subject required for the corresponding interim analysis has been randomized.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment, matching study drug kits (1 bottle per subject) for the subject and PK sampling group (for the subcohort and for the first 12 subjects in each age group in Cohort 1). The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contacts the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF. The documentation received from the IWRS indicating the code break is filed in the central Trial Master File.

6. DOSAGE AND ADMINISTRATION

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. Subjects randomized to a placebo regimen are subsequently randomized in a 1:1 ratio to receive placebo matching either the volume of the high or of the low dose. Doses are based on weight and age group (3 age groups [≥28 days and <3 months; ≥3 months and <6 months, or ≥6 months and ≤3 years of age] are defined depending on the subject's age at the time of consent). An overview of the treatments for Cohort 2 newly recruited subjects is provided in Table 3.

Table 3: Treatment Overview

Treatment		Age Group[a]	Dosing Regimen[b,d]	Volume
High dose		1	2.5 mg/kg bid on Days 1 to 7	A mL[c] oral suspension of JNJ-53718678
		2	3.0 mg/kg bid on Days 1 to 7	C mL[c] oral suspension of JNJ-53718678
		3	4.5 mg/kg bid on Days 1 to 7	E mL[c] oral suspension of JNJ-53718678
Low dose		1	0.85 mg/kg bid on Days 1 to 7	B mL[c] oral suspension of JNJ-53718678
		2	1.0 mg/kg bid on Days 1 to 7	D mL[c] oral suspension of JNJ-53718678
		3	1.5 mg/kg bid on Days 1 to 7	F mL[c] oral suspension of JNJ-53718678
Placebo	Match high dose	1,2, or 3	placebo bid on Days 1 to 7	A, C, or E (respectively) mL[b] placebo
	Match low dose	1,2, or 3	placebo bid on Days 1 to 7	B, D, or F (respectively) mL[b] placebo

a. Age Group 1: ≥28 days and <3 months; Age Group 2: ≥3 and <6 months; Age Group 3: ≥6 months and ≤3 years.
b. Doses are provided for JNJ-53718678-AAA.
c. A to F represents the volume of oral JNJ-53718678 suspension to obtain the required dose of JNJ-53718678-AAA or the volume of the matching placebo suspension. JNJ-53718678 is formulated as an oral suspension containing 23 mg/mL microfine JNJ-53718678-ZCL, the hemi-tartrate salt of JNJ-53718678-AAA, which is equivalent to 20 mg/mL JNJ-53718678-AAA, to be used depending on the bodyweight of the subject (and the required volume to be administered). The required volume to be administered per intake will be calculated by the IWRS and provided to the sites.
d. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total.

Study drug administration should start as soon as possible, but no later than 4 hours after randomization and within 5 days after symptom onset. For analysis purposes, the day of first study drug intake will be considered Day 1.

Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. The study drug can be administered with/without food. The study drug will be administered orally using a dosing syringe. For Cohort 1 and during hospitalization, the drug can also be administered through a nasogastric tube, if already in place.

Note: Prior to Protocol Amendment 4, the total daily dose was the same but the daily dosing frequency was qd instead of bid.

- Cohort 1:

  During hospitalization: the study drug will be administered by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel. Date and time of dosing will be recorded by the site staff.

  After Discharge: parent(s)/caregiver(s) will administer study drug at home if the subject is discharged prior to Day 7. Date and time of dosing will be captured in the study

medication log, to be completed by the parent(s)/caregiver(s) in the provided electronic device.

- Cohort 2, the first dose of study drug will be administered, by the study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel, at the study site. On Day 1, date and time of dosing will be recorded by the site staff. At home, date and time of dosing will be captured in the study medication log, to be completed by the parent(s)/caregiver(s) in the provided electronic device.

Study site personnel will instruct subjects' parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing as per sponsor provided investigational product preparation instruction (IPPI).

7. STUDY DRUG COMPLIANCE

During hospitalization, study drug will be administered orally or via nasogastric tube (if applicable) under supervision of study-site personnel at the study-site.

After discharge, if this occurs prior to the end of the dosing period, and in Cohort 2, study drug will be administered orally by the subject's parent(s)/caregiver(s) at home. At the screening visit, the subject's parent(s)/caregiver(s) will receive instructions on compliance with study drug administration, and this instruction will be repeated at the time of discharge, if applicable. At home, dosing will be recorded by the parent(s)/caregiver(s) in the electronic study medication log (Attachment 6). For Cohort 2, site staff should review the entries of the electronic study medication log daily to ensure compliance with administration of study drug. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject's parent(s)/caregiver(s) who is (are) not compliant with administering the study drug.

If the subject vomited, regurgitated, or did not completely swallow the study drug, this information should be recorded and the subject should not be redosed.

In case a dose was missed, the dose should be given as soon as possible, but within 6 hours after the scheduled time. If more than 6 hours has elapsed, the dose should be skipped and the next dose should be given at the next scheduled timepoint per the initial dosing schedule.

If subjects are rehospitalized (subjects from Cohort 1 after discharge) and or hospitalized (subjects from Cohort 2) due to worsening of RSV disease during the treatment period, administration of study drug should continue.

An overdose in this study is defined as the administration of a volume of the study drug above that of the total daily calculated volume for the respective age and bodyweight-based dose within a 24-hour time period.

8. CONCOMITANT THERAPY

Concomitant medications, except those listed below, are allowed during this study. All concomitant medications and supportive therapy (prescription or over-the-counter medications,

including vaccines, vitamins, herbal supplements, and non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, physiotherapy) different from the study drug must be recorded in the eCRF, from the date the ICF is signed through to the end-of-study visit. Recorded information will include a description of the type of the drug/therapy, treatment duration (dates of treatment start and stop), dose regimen, route of administration, and its indication. Modification of an effective pre-existing chronic therapy should not be made for the explicit purpose of entering a subject into the study; however, if a subject has received acute doses of a prohibited drug, switching to an alternative drug chosen at the discretion of the investigator will be allowed.

All hospitalized subjects will receive supportive care per local institution standards and applicable guidelines. While treatment guidelines and standards vary based on local practice and should be considered in the management of subjects, within the parameters of this study, it is recommended that supplemental oxygen can be administered or withdrawn, as appropriate, to maintain an SpO_2 ≥93% as long as it is medically indicated (for subjects whose SpO_2 is ≥93% when clinically stable).

Subjects can receive medications such as acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs, leukotriene antagonists, or antihistamines, considering their respective package insert, at the investigator's discretion prior to and during the study. However, in line with the clinical practice guidelines and package inserts, it is recommended to limit the use of antitussives and mucolytics, in particular in the younger age group. In case these medications are used, the PRESORS should report the worst symptom(s) during the recall period.

Subjects whose mother received an investigational RSV vaccination during the pregnancy for this child and whose age is <3 months at time of screening will not be allowed in the study.

In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics (see Section 9.2.2). Parents/caregivers should be instructed accordingly.

Fexofenadine is allowed, taking into account its package insert and dosing instructions for use in children, but JNJ-53718678 may reduce the fexofenadine exposure by 65% and reduce its efficacy if administered simultaneously. To limit the reduction in efficacy it is recommended to administer fexofenadine at least 1 to 2 hours before taking JNJ-53718678 and/or at least 4 hours after taking JNJ-53718678, taking into account the local prescribing info for fexofenadine.[13,15]

Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted, including:

- inhaled β-agonists or anticholinergics
- oral/intravenous/intramuscular antibiotics such as β-lactams

Note: The temporary use of over-the-counter medications in the 14 days prior to randomization is permitted. The use of vitamins and mineral supplements is also permitted.

The following medications are not permitted during the study and for the time period prior to screening as noted:

- herbal supplements with active metabolic enzyme inducing components (eg, St-John's Wort) within 21 days or BCRP (a transporter protein) inhibiting components (eg, curcumin) within 2 days prior to randomization and during the study except for topically administered products.
- prescription medications intended to prevent or treat the RSV infection itself (eg, ribavirin, IV immunoglobulin, palivizumab) within 14 days prior to screening and during the study. Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.
- prescription medication eltrombopag, a known BCRP inhibitor, within 2 days prior to randomization and during the study.
- the following prescription medications with 14 days prior to screening, until 3 days after last dose:

  Prescription medications which are known to be a moderate or strong inhibitor of cytochrome P450 (CYP)3A4 enzymes, such as, but not limited to, macrolide antibiotics.

  Prescription medications that are known to be strong inducers of CYP3A4 such as, but not limited to, rifampin.
- Medications with a known risk to prolong the QT interval[14] and not belonging to the class of moderate or strong CYP3A4 inhibitors (eg, azithromycin, a mild CYP3A4 inhibitor with known QT prolonging risk) can be continued if the subject is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, however, the use of these medications cannot be initiated at screening and/or during the study intervention treatment period.
- Systemic corticosteroids if used for >7 consecutive days immediately prior to randomization at doses higher than 2 mg/kg/day of prednisone or equivalent. Subjects meeting the eligibility criteria at screening but requiring initiation or increased doses of systemic corticosteroids (>2 mg/kg/day of prednisone or equivalent) for a prolonged period (>7 consecutive days) during the study are allowed to continue participation in the study.
- Any other investigational drug within 30 days or 5-fold half-lives of that drug (whichever is longer) prior to screening and during the study.
- Any investigational vaccine, including investigational RSV vaccines, at any time prior to and during the study. Routine vaccinations are permitted during the study but local guidelines have to be followed.
- Any investigational medical device.
- Prior exposure to JNJ-53718678 at the time of screening.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of antiviral effect, clinical course, safety, PK, biomarker, acceptability and palatability, and medical resource utilization assessments applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: noninvasive procedures should be collected first before invasive procedures (ECG first, then vital signs/SpO_2, then mid-turbinate nasal swab, and blood draw last). However, mid-turbinate nasal swabs for RSV RNA viral load should be kept as close to the specified time as possible. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Medical resource utilization data will be collected. Refer to Section 9.6 [Medical Resource Utilization] for details.

The maximum amount of blood drawn from each subject in this study will not exceed 9.2 mL over the duration of the study in line with recommendations collated by the WHO[12].

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

An electronic device to be used for the parent(s)/caregiver(s) PRESORS (Attachment 5), study medication log (Attachment 6), nasal swab log (Attachment 7), temperature log (Attachment 8), and the Study Medication Tolerability Assessment (Attachment 9) will be provided to the parent(s)/caregiver(s) at the time of screening to record parent(s)/caregiver(s) ratings of the severity of the subject's symptoms every day (bid or qd), as specified in the TIME AND EVENTS SCHEDULE. The investigator/study staff will provide sufficient information (included in the study manual) to enable the parent(s)/caregiver(s) to complete the different logs and parent(s)/caregiver(s) PRESORS on the electronic device correctly and on schedule to avoid missing or incorrect data. Prior to completing the screening assessment, the parent(s)/caregiver(s) must complete a training module (included on the electronic device) on how to enter responses to questions on the electronic device.

In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parents/caregivers should be instructed accordingly.

In case antitussives and mucolytics are used, the PRESORS should report the worst symptom(s) during the recall period.

Assessments, which should be performed around the dosing timepoint as per the TIME AND EVENTS SCHEDULE, should be done prior to actual first dosing on Day 1 and preferably prior to dosing on the other days.

9.1.2. Screening Phase

The procedures specified in the TIME AND EVENTS SCHEDULE will only be performed after the parent(s)/caregiver(s)' written informed consent has been obtained and have to occur before randomization (refer to Section 16.2.3).

If needed, and depending on the time of presentation, screening/predose assessments and establishment of eligibility can continue the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility. For analysis purposes, the day of first study drug intake will be considered Day 1.

Screening will be completed and randomization as well as first dosing will be performed within 5 days after the onset of RSV symptoms to ensure the eligibility of the subject. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility (see below). Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first.

Blood samples for biochemistry (including creatinine clearance calculated by the GFR formula (Schwarz equation), hematology and a urine sample for urinalysis will be collected at screening and analyzed at the central laboratory (for urine samples only in case of dipstick abnormalities). Given the absence of safety signals regarding laboratory findings in previous studies, the importance of starting treatment as soon as possible after symptom onset, and the required turn-around time for central testing, treatment can be initiated prior to availability of the lab results.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate) and a standard triplicate 12-lead ECG will be recorded (approximately 1 minute apart and preferably all within 5 minutes) as specified in the TIME AND EVENTS SCHEDULE and a complete physical examination (CPE; including all body systems) will be performed. Physical examination also includes the collection of body weight, length, and head circumference.

Baseline demographics, medical history, and family history with regards to risk factors for wheezing/asthma will be recorded in the eCRF of this study.

Concomitant disease and medication will be recorded and AE recording will start.

At screening, a nasal (preferentially mid-turbinate) predose swab will be collected for local RSV diagnosis using a preferably rapid PCR- or other molecular-based diagnostic assay (preferred), or a rapid antigen-detection-assay. If a subject had a positive similar RSV diagnostic test from another study for which (s)he was otherwise ineligible or a SOC test within 24 hours prior to start of screening and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility. Randomization should occur within 24 hours after start of screening or within 48 hours after collection of the SOC sample used for local RSV diagnosis, whichever comes first. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main ICF or with the diagnostic study ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central

laboratory for additional virologic analyses, as applicable. In case the local PCR detects more than 1 virus, the subject is eligible as long as RSV is one of the viruses detected.

After randomization, but immediately predose, a mid-turbinate nasal swab will be collected, aliquoted and sent to the central lab for:

- RSV diagnosis confirmation using a PCR-based assay
- RSV viral load
- Examination for the presence of viral or bacterial co-infection using multiplex PCR sequencing
- Viral sequencing

  Note: Leftover samples will be stored in the biobank for biomarker research if warranted.

If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL each).

Parent(s)/caregiver(s) will be provided with the electronic device at the time of screening and will be instructed by the site staff on how to complete the different logs and the parent(s)/caregiver(s) PRESORS, rating the severity of signs of RSV, and noting the impact of RSV on the subject's household. Parent(s)/caregiver(s) will complete a brief training on the electronic device on how to complete the different logs and the parent(s)/caregiver(s) PRESORS before they will be allowed to complete their first entry in the electronic device.

Clinical evaluation will be performed. For both cohorts, this includes but is not limited to measurements/evaluations of respiratory rate, body temperature, SpO_2, and need for antibiotics. For Cohort 1, this additionally includes but is not limited to level of and duration of hospital care, duration of hospitalization, hydration/feeding by IV line/nasogastric tube, while for Cohort 2, this additionally includes the evaluation of the need for and duration of hospitalization. Note that for all cohorts, all clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding).

9.1.3. Double-Blind Treatment Phase

Assessments to be performed during the treatment phase are specified in the TIME AND EVENTS SCHEDULE

Day 1/Day of Randomization

Eligible subjects will be randomized on Day 1, which is preferable the same calendar day as the screening visit. Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within 5 days after RSV symptom onset and within 24 hours after start of screening or within 48 hours after collection of the SOC sample for local RSV diagnosis, whichever comes first. All subjects (both cohorts) will be administered the first

dose of the study drug at the study site on Day 1, by or under supervision of the study site personnel, immediately after the predose swab.

Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For subjects who receive only 1 dose of JNJ-53718678 or placebo PM on Day 1, dosing should continue through the morning (ie, AM) of Day 8 so that all subjects receive 14 consecutive doses in total. Administration of the second dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule.

Assessments to be performed on Day 1, and their timing are specified in the TIME AND EVENTS SCHEDULE.

Day 2 to Day 8 (End of Treatment)

Subjects will receive 14 doses in total, administered twice daily and preferably at approximately the same time each day for both intakes (see above).

For Cohort 1 (prior to discharge) and for Cohort 2, study-site personnel will instruct subject's parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing.

Between Day 2 and Day 8, the assessments that will be performed at predefined timepoints (different for Cohort 1 and Cohort 2) are specified in the TIME AND EVENTS SCHEDULE. For Cohort 1, some of these assessments will only be performed if and while the subject is hospitalized as indicated in the TIME AND EVENTS SCHEDULE.

For Cohort 1 subjects after discharge and for Cohort 2 subjects, some of these assessments will be performed during on-site visits (Day 3, 5 and 8) as indicated in the TIME AND EVENTS SCHEDULE. These scheduled study visits if feasible for the study site and if allowed per local regulations, can also be done as home visits. The subcohort of Cohort 1 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 (see Section 9.4.1). The first 12 subjects in each age group (excluding the subcohort) in Cohort 1 will be assigned a specific PK sampling schedule (see Section 9.4.1)

Investigational staff will review daily the completion of the parent(s)/caregiver(s) PRESORS and the logs once data is transmitted to the database from the electronic device and will contact the parent(s)/caregiver(s) in case of incompliance. For Cohort 2, site staff should review the entries of the electronic study medication log daily to ensure compliance with administration of study drug.

9.1.4. Posttreatment Phase (Follow-Up)

For all cohorts, subjects will be evaluated for a total of approximately 28 (±3) days post randomization

Both Cohort 1 subjects after discharge and Cohort 2 subjects will be required to return to the site for follow-up assessments as an outpatient on Day 14 and Day 21, as indicated in the TIME AND

EVENTS SCHEDULE. These scheduled study visits if feasible for the study site and if allowed per local regulations, can also be done as home visits. On Day 28 (±3), subject's parent(s)/caregiver(s) will be contacted by the site staff for a telephone follow-up visit. In case a subject is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 21 Follow-Up Visit, parent(s)/caregiver(s) might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit for the subject at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28 (±3). Only clinically relevant assessments will be performed during this visit, as applicable.

During the follow-up phase, for both cohorts, the parent(s)/caregiver(s) will complete the parent(s)/caregiver(s) PRESORS as of Day 9 through Day 14 twice a day (morning and evening; see TIME AND EVENTS SCHEDULE. From Day 15 through Day 21, the parent(s)/caregiver(s) will complete the parent(s)/caregiver(s) PRESORS once daily, in the evening, with the final parent(s)/caregiver(s) PRESORS assessment being scheduled at the Day-21 on-site visit (see TIME AND EVENTS SCHEDULE). Investigational staff will review daily the completion of the parent(s)/caregiver(s) PRESORS once data is transmitted to the database from the electronic device and will contact the parent(s)/caregiver(s) in case of incompliance. Investigational staff will also instruct parent(s)/caregiver(s) on the continuation of the collection of nasal swabs, as applicable (see Section 3.1).

For all cohorts, in case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. Assessments will be performed as indicated in the TIME AND EVENTS SCHEDULE.

9.2. Efficacy Evaluations

9.2.1. Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal mid-turbinate swab samples will be measured at the central lab using a qRT-PCR assay. Mid-turbinate swab specimens for the determination of RSV viral load will be collected at several timepoints during the study as indicated in the TIME AND EVENTS SCHEDULE. Date and time of sampling will be collected. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). The nostril that was sampled will be documented by the site staff (nasal swabs taken on-site) or by parent(s)/caregiver(s) (nasal swabs taken at home).

On Day 1, in both cohorts, the mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study drug. The next swabs should be collected from the

same nostril preferably at approximately the same time as the predose swab taken on Day 1 and preferably prior to dose administration.

- Cohort 1:

  During hospitalization: Swabs will continue to be collected each day during hospitalization through Day 13 or until discharge (whichever comes first).

  Discharged subjects: After discharge, swabs will be collected daily through Day 8 in all subjects. As of Day 8, in subjects who were symptomatic based on clinician PRESORS at Day 8, daily swabs will be collected through Day 13 or until the subject becomes asymptomatic based on the parent(s)/caregiver(s) PRESORS, as evaluated by the investigational staff (whichever comes first).

- Cohort 2: Swabs will be collected daily through Day 8 in all subjects. As of Day 8, in subjects who were symptomatic based on clinician PRESORS at Day 8, daily swabs will be collected through Day 13 or until the subject becomes asymptomatic based on the parent(s)/caregiver(s) PRESORS, as evaluated by the investigational staff (whichever comes first).

On Day 14 and Day 21, a swab will be collected during the scheduled visit for all subjects.

The investigational staff will collect mid-turbinate swabs during the scheduled (on-site) visit (Cohort 1 after discharge and Cohort 2) or during hospitalization (Cohort 1). When no on-site visit is scheduled per the TIME AND EVENTS SCHEDULE, it may be agreed between the study site and parent(s)/caregiver(s) to perform a visit for nasal sampling purposes only, or send an HCP to the subject's home for collection of the nasal swab sample. In case collection by an HCP is not possible, the investigator/study site personnel will train the parent(s)/caregiver(s) to collect the mid-turbinate nasal swab. The training to collect and document nasal swabs will be done at screening, and repeated before discharge if needed for Cohort 1.

The collection of these nasal swab and date and time of sampling should be recorded for all subjects in the eCRF or in the nasal swab log on the electronic device (see Attachment 7), as described in the eCRF completion guidelines and the completion guides for the electronic device, which will be provided to the investigator (see Section 15).

All parent(s)/caregiver(s), after being properly trained, will be provided with appropriate mid-turbinate nasal swabs and Universal Transport Medium (same supplies as those used to collect nasal samples at the sites) to collect mid-turbinate nasal swabs. All swabs collected at home by the parent(s)/caregiver(s) should be stored immediately between 2°C and 8°C (in the refrigerator) and brought to the site at the next scheduled visit.

Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

RSV RNA viral load can also be 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 SOC, which may be used to assess virologic parameters.

The RSV infectious virus load as measured by quantitative culture of RSV (plaque assay), if feasible, on selected nasal swab samples, may be used to assess virologic parameters.

9.2.2. Clinical Course of RSV Infection

The study will include the following evaluations of the clinical course of RSV infection:

- Cohort 1 and Cohort 2:

  clinical parameters: respiratory rate, heart rate, SpO_2, and body temperature as measured by the investigator during scheduled visits. ***Note:*** If the subject is enrolled in the substudy of Study 53718678RSV2002 (see Section 3.1), the same parameters as assessed by the biosensor will be recorded from the standard-of-care monitoring/assessments as part of the substudy assessments (refer to the substudy Clinical Protocol for detailed information) at the timepoints indicated in the TIME AND EVENTS SCHEDULE.

  body temperature as measured by parent(s)/caregiver(s) and recorded in the temperature log (Attachment 8) (for Cohort 1 after discharge and Cohort 2)

  evolution and severity of signs and symptoms of RSV disease (fever, cough, sputum, wheezing, difficulty breathing, nasal congestion, feeding issues) as assessed by the parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) and the clinician (clinician PRESORS)

  the need for (re)hospitalization

  the occurrence of complications, bronchiolitis, or viral pneumonia with onset after treatment initiation that are associated with RSV per investigator assessment

  the need for antibiotics related to complications associated with RSV per investigator assessment

- Cohort 1 only:

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

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

  level of and duration by level of hospital care (eg, ICU, transitional care unit, ward floor)

  oxygen requirement type (eg, supplemental oxygen, noninvasive pressure ventilation, endotracheal-mechanical ventilation), and duration

  hydration and feeding by IV line/nasogastric tube and duration

Note*:* In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parents/caregivers should be instructed accordingly.

Note*:* In case antitussives and mucolytics are used, the PRESORS should report the worst symptom(s) during the recall period.

Clinical outcome assessments as performed separately by the clinician (clinician PRESORS) and the parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS, temperature log) will be captured in an electronic device. Symptoms reported in these assessments will not be reported as AEs but constitute a part of the efficacy evaluations.

An electronic device will be provided to the subject's parent(s)/caregiver(s) at the time of screening, after enrollment of the subject. The investigator/study site personnel will provide sufficient information to enable the subject's parent(s)/caregiver(s) to complete these assessments. The parent(s)/caregiver(s) PRESORS assessment should be completed once at screening, then bid (in the morning and in the evening) from Day 1 (day of first dose) to Day 14 and then once daily in the evening until the Day 21 visit. The final parent(s)/caregiver(s) PRESORS assessment has to be completed during the scheduled Day-21 on-site visit (see also TIME AND EVENTS SCHEDULE). The first parent(s)/caregiver(s) PRESORS of the bid schedule on Day 1 needs to be completed as close as feasible and prior to the first administration of study drug. The screening parent(s)/caregiver(s) PRESORS assessment will be accepted as baseline if completed within 4 hours before randomization.

During hospitalization (Cohort 1), body temperature will be measured by the investigator. On the day of discharge (Cohort 1) or at screening (Cohort 2), the initial measurement of body temperature should be performed by the investigator. If discharged (Cohort 1) or screened in the morning, only the evening assessment of the bid schedule for the measurement of body temperature should be recorded in the temperature log on the electronic device (Attachment 8).

The parent(s)/caregiver(s) PRESORS and temperature log should preferably be completed by the same person throughout the study. A second parent/caregiver who frequently provides direct care of the child can be set up as a backup reporter on the electronic device to ensure assessments are recorded if the primary parent/caregiver is unable to enter information for any reason.

Investigational staff will review daily the completion of the parent(s)/caregiver(s) PRESORS and logs once data is transmitted to the database from the device. The site will contact the parent(s)/caregiver(s) in case if parent(s)/caregiver(s) PRESORS and information collected in the logs are not uploaded according to the schedule, which might be due to issues with the electronic device or due to non-compliance. The site will monitor and help the parent(s)/caregiver(s) to be compliant. Investigational staff will also instruct parent(s)/caregiver(s) on the continuation of the collection of nasal swabs, as applicable.

9.2.3. Viral Sequencing

Sequencing data will not be reported to the investigators. Viral resistance will be monitored by sequencing of the F-gene of the viral genome in all baseline nasal swab samples and in subsequent samples upon request of the sponsor's virologist. Other regions of the RSV genome may also be sequenced at discretion of the sponsor's virologist. The impact of the viral subtype and baseline genotype on the antiviral response will be explored. Sequencing results may be presented in a separate report.

Changes in viral sequence will be evaluated but will not be reported as AEs.

9.3. Safety Evaluations

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity (end of study/early withdrawal).

Details regarding the IDMC are provided in Section 11.12.

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

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

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

Adverse Events

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

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

Exacerbations of underlying pulmonary disease occurring after treatment start, otitis media, bronchiolitis, viral pneumonia, bacterial superinfections of presumed respiratory origin per investigator assessment, and exacerbations of underlying cardiovascular conditions should be reported as AE and are considered events of interest (complications associated with RSV per investigator assessment). For each reported event, investigators will be asked if they consider the event to be a complication of or associated with RSV. When answered yes, additional data related to that event is collected when available. Further details on these events of interest will be captured separately in the eCRF.

Clinical Laboratory Tests

Blood samples for serum chemistry, hematology, and a urine sample for urinalysis will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

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

Any values that indicate a potential safety concern will be assessed by the investigator and appropriate follow-up actions, including potential discontinuation from treatment (see also Section 10.3, will be carried out.

The following tests will be performed by the central laboratory:

- Hematology Panel

-hemoglobin
-hematocrit
-RBC count
-reticulocyte count
-RBC parameters:
  * mean corpuscular hemoglobin (MCH)
  * MCH concentration
  * mean corpuscular volume
-WBC count
-WBC differential:
  * neutrophils
  * lymphocytes
  * monocytes
  * eosinophils
  * basophils
-platelet count

Note: A white blood cell (WBC) evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.
In addition, any other abnormal cells in a blood smear will also be reported.

- Serum Chemistry Panel

-alkaline phosphatase
-ALT
-AST
-bicarbonate
-uric acid
-chloride
-magnesium
-creatinine
-glucose
-potassium
-sodium
-total bilirubin (direct and indirect)
-urea

- eGFR will be calculated/reported by the central lab (Schwarz formula)
- Urinalysis

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

Dipstick will be performed at the site as per the TIME AND EVENTS SCHEDULE. If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment, in the central lab. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.

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 should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) may be required. During the study locally determined potassium and/or magnesium levels need to be recorded in the eCRF as unscheduled laboratory visits/assessments.

At Screening (Study Day -1 through 1), a nasal (preferentially mid-turbinate) predose swab will be collected for RSV diagnosis. Swabs collected per local SOC testing within 24 hours prior to start of screening may be used in determining study eligibility. If a rapid-antigen-detection assay is used as part of SOC or study-specifically (with the main ICF or with the diagnostic study ICF having been signed), the remainder of the screening sample used for the RSV diagnostic testing should be sent to the central laboratory for additional virologic analyses, as applicable.

After randomization (immediately predose), a mid-turbinate nasal swab will be collected, aliquoted and sent to the central lab for RSV diagnosis confirmation, assessment of viral load and for the presence of viral or bacterial co-infection, and viral sequencing. If a study-specific screening nasal mid-turbinate swab was collected within 8 hours prior to dosing, the leftover of that sample can serve as the baseline sample and should be shipped to the central laboratory, provided that the study-specific nasal mid-turbinate screening sample was stored appropriately and has sufficient sample volume available (minimum 4 aliquots of 600 µL).

Electrocardiogram (ECG)

Screening and on-treatment ECGs will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE.

Electrocardiograms (triplicate 12-lead ECG; approximately 1 minute apart and preferably all within 5 minutes) should be performed using procedures commensurate with the subject's age.

For eligibility determination, the machine read ECG results, printed on the ECG device print-out of the ECG tracing, will be taken into account. The subject should have a QTcF interval ≤450 ms per the machine read parameter result (mean of triplicate). If the QTcF interval is confirmed >450 ms per the machine read parameter result (mean of triplicate) by repeat ECG recording during screening (see Section 4.2), the subject is ineligible.

Central ECG readings will be performed by a central ECG lab. Instructions for ECG acquisition and ECG transmission will be described in the manual provided by the ECG lab. There will be 2 ECG reports: a preliminary report and a final report. Both ECG reports generated by the central ECG lab will need to be interpreted for clinical significance, signed and dated by the investigator, and filed in the subject's medical record. Clinically relevant abnormalities occurring during the study should be recorded by the investigator in the AE section of the eCRF.

In the event that an invasive procedure such as a blood draw or nasal swab and an ECG are required at approximately the same time, ECGs should be collected first. Electrocardiograms may be repeated at the investigator discretion.

The investigator will be responsible for evaluating the results and determining if any findings are of clinical significance. If a subject has a QTcF interval ≥500 ms based on a machine read ECG result (mean of triplicate), confirmation needs to be obtained by repeat ECG recording during the same visit day. If confirmed based on the repeat machine read ECG results (mean of triplicate), the subject needs to be withdrawn from study treatment (see also Sections 9.3.1 and 10.3). In case other clinically relevant ECG abnormalities are observed post baseline a confirmatory ECG must be performed preferably within 48 hours, but no later than 72 hours, after the results have become available. Evaluation of clinical relevance should be done on confirmed results.

Vital Signs (blood pressure)

For the duration of hospitalization, vital signs will be assessed for each subject twice daily preferably at approximately the same time on each scheduled day (see TIME AND EVENTS SCHEDULE). After discharge, vital signs will be assessed once during the on-site visits (see TIME AND EVENTS SCHEDULE).

Blood pressure will be assessed sitting or supine (preferably the same position at each measurement), with a completely automated device. Manual techniques will be used only if an automated device is not available.

Clinically relevant abnormalities in blood pressure occurring during the study should be recorded in the AE Section of the eCRF.

Physical Examination

To evaluate the subject's eligibility, a CPE and measurements of length, head circumference, and body weight will be performed at screening, and a directed physical examination (DPE) will be performed at several time points throughout the study (see TIME AND EVENTS SCHEDULE).

A DPE includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.

A skin examination includes an examination of the mucous membranes, but does not include a vaginal or rectal exam. However, if the subject develops a cutaneous reaction/rash, vaginal and rectal exams may be done if clinically relevant.

To obtain the actual body weight, subjects are advised to be weighed unclothed with a dry diaper only or lightly clothed, with consistency for all visits. Length may be assessed in the supine position and the same position should be used for the subsequent assessments of that subject.

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

9.3.1. Specific Toxicities and Safety Topics of Special Interest

The following only applies to AEs starting after initiation of study treatment.

AST and ALT Elevation

Management will be at the discretion of the investigator and should follow generally accepted medical standards. Grading of AST and alanine transaminase (ALT) elevation will be based on the DMID Pediatric Toxicity Table (see Attachment 1).

For Grade 3 or 4 laboratory abnormalities, subjects should have a confirmatory measurement, preferably within 48 hours after the laboratory results become available to the site. The below management scheme is for confirmed laboratory abnormalities and not for isolated events.

Grade 1 (1.1 to <2.0x ULN), or Grade 2 (≥2.0 to <3.0x ULN)

Subjects may continue the intake of study drug.

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

Grade 3 (≥3.0 to ≤8.0x ULN), or Grade 4 (>8.0x ULN)

If occurring during the treatment period, subjects will permanently discontinue the intake of study drug, although with continuation of appropriate safety follow-up visits.

It is recommended that the investigator contacts the sponsor to discuss the case. Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.

RSV-related Complications

Management will be at the discretion of the investigator and should follow generally accepted medical standards.

Cardiac Events Potentially Related to QT Prolongation

Regular cardiac safety monitoring will be done in this study via assessments of AEs, laboratory abnormalities, and regular ECGs.

A subject's study intervention must be discontinued if the subject has a QTc value ≥500 ms at any scheduled visit based on a machine read ECG result (mean of triplicate), confirmed by repeat ECG recording during the same visit day (see Section 9.3). For subjects with a confirmed QTc interval value ≥500 ms, the following measures should be taken:

- The cardiac event must be reported to the sponsor within 24 hours.
- The investigator should request urgent cardiology referral, within 24 hours if possible.
- Clinical evaluation including safety biochemistry (such as electrolytes), assessment of the use of concomitant QT prolonging drugs, and evaluation for the presence of any structural heart disease must be conducted. Levels of potassium and magnesium to be determined by the central laboratory.
- If hypokalemia or hypomagnesemia is identified, the levels of potassium and/or magnesium should be checked as soon as possible at the local laboratory and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at local laboratory) is required. During the study, locally determined potassium and/or magnesium levels need to be recorded in the eCRF as unscheduled laboratory visits/assessments.
- An ECG should be repeated every 24 hours until resolution of QTc interval prolongation is confirmed. The subject's condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled visits/assessments.

9.4. Pharmacokinetics

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a population PK approach by means of nonlinear mixed-effects modeling.

9.4.1. Evaluations

Blood samples for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick at the timepoints indicated in the TIME AND EVENTS SCHEDULE. 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 (see Table 4). 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 (see Table 4). 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 at this site.

Table 4: Overview of Pharmacokinetic Sampling Windows for Cohort 1 Subjects

Pharmacokinetic Sampling Group	Visit Day 1	Visit Day 2	
	Time after dose intake at Visit 1	Time before dose intake at Visit 2	Time after dose intake at Visit 2
X	2 h – 5 h	-	30 min – 3 h
Y	5 h – 9 h	3 h – 1 min	-

For the subjects recruited to Cohort 2 after Protocol Amendment 4, PK samples will be collected approximately one hour after administration of study drug (after the ECGs are obtained if applicable) at Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

Samples may also be used for the analysis of metabolites of JNJ-53718678 or endogenous markers for enzymes or transporters involved in the metabolism and distribution of JNJ-53718678, at the discretion of the sponsor. Blood samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. The subject's confidentiality will be maintained.

The following information needs to be recorded on the requisition form and/or eCRF: date and time of preceding study drug intake, date and time of PK blood sampling, fed status (yes/no, fed status defined as having a meal 30 minutes before or 30 minutes after dosing), and type of meal (milk vs. other).

9.4.2. Analytical Procedures

Bioanalysis will be performed on these samples (applicable treatment groups only [not the placebo group]) to determine blood concentrations of JNJ-53718678 using a validated, specific and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method under the supervision of the sponsor's department of Bioanalysis. If applicable, metabolite concentrations may be determined using a qualified LC-MS/MS method under the supervision of the sponsor's department of Bioanalysis.

Based on the individual concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-53718678 will be derived using popPK modeling, including, but not limited to: AUC, C_{trough}, and possibly C_{max}. Baseline covariates (eg, body weight, age, sex, race) may be included in the model, if relevant. Other PK parameters may be determined at the discretion of the sponsor if deemed useful to evaluate the PK of JNJ-53718678.

PK parameters for other analytes (eg, metabolites, endogenous markers) may be determined at the discretion of the sponsor and may also be subjected to popPK modeling.

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

Obtained PK and PD data (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be used to explore the relationship between the PK and PD parameters.

9.6. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Assessments performed as part of the clinical course of RSV infection-related assessments (see Section 9.2.2)

  Duration of hospitalization (total days length of stay, including duration by wards level [eg, ICU]) (Cohort 1 only).

  The number of subjects (proportion) who started antibiotic use after the first dose of study drug through the last study visit.

  Requirement for, and duration of, hospital (re)admission for respiratory reasons through the last study visit.

- Additional assessments

  Number and duration of medical care encounters and treatments (including physician or emergency room visits, tests and procedures, and medications, surgeries and other selected procedures; inpatient and outpatient).

9.7. Acceptability and Palatability

Acceptability and palatability of the JNJ-53718678 formulation will be assessed through a questionnaire completed by parent(s)/caregiver(s) in the electronic device after last dosing. See Attachment 9.

9.8. Biomarkers

Leftover mid-turbinate nasal swab and blood samples collected for other testing may be used for exploratory biomarker analyses (eg, proteins including cytokines, microbiome), on the premise that these markers may play a role in the treatment response, safety of JNJ-53718678, or RSV-related disease.

Analyses of biomarkers may be performed at the sponsor's discretion and reported separately from this study.

No human deoxyribonucleic acid (DNA) analyses will be performed on these samples.

9.9. Other Evaluations

Mid-turbinate nasal swabs collected immediately prior to first dosing will be used to determine the presence of viral (other than RSV) or bacterial pathogens (both by multiplex PCR) at the central laboratory.

9.10. Sample Collection and Handling

The actual dates and times of sample collection will be collected in the eCRF or laboratory requisition form.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections. For mid-turbinate nasal swabs, the date and time of sampling, as well as which nostril was sampled, should be recorded for all subjects in the eCRF or in the nasal swab log on the electronic device (see Attachment 7), as described in the eCRF completion guidelines and the completion guides for the electronic device, which will be provided to the investigator (see Section 15). For Cohort 1 (prior to discharge) and for Cohort 2 (at screening or Day 1 at the latest), the investigator/study staff will provide instructions to the parent(s)/caregiver(s) and will train them on how to document this correctly on the electronic device.

All swabs collected at home by the parent(s)/caregiver(s) should be stored immediately between 2°C and 8°C (in the refrigerator) and brought (cooler bag) to the site at the next scheduled visit.

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

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY DRUG/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the treatment phase if he or she has completed dosing on the 7 days of the dosing period and the Day 8 visit. A subject is considered to have completed the study if he or she has also completed assessments of the last follow-up visit on Day 28.

10.2. Stopping Criteria

10.2.1. For an Individual Subject

See Section 10.3, Discontinuation of Study Treatment.

10.2.2. For the Study

Further enrollment or dosing in the study will be discontinued by sponsor decision at recommendation of the IDMC when the IDMC considers an event or multiple events to represent an unacceptable risk to the health and well-being of subjects.

Further enrollment in the study will be discontinued by sponsor decision at recommendation of the IDMC based on their review of the interim analysis results for safety, PK and efficacy.

10.3. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue study drug before the end of the treatment regimen.

If subjects are rehospitalized (subjects from Cohort 1 after discharge) and or hospitalized (subjects from Cohort 2) due to worsening of RSV disease during the treatment period, administration of study drug should continue.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug
- The subject experiences a Grade 3 rash or higher
- The subject has a QTcF interval ≥500 ms based on a machine read ECG result (mean of triplicate), confirmed by repeat ECG recording during the same visit day (see Section 9.3.1)
- The subject is reported with the following laboratory abnormalities: AST or ALT increases ≥3 x ULN in samples taken at screening, confirmed in a repeat test, to be performed within 48 hours of the result being available at the site
- The subject is reported with any other laboratory abnormality of Grade 3 or 4 at screening, confirmed in a repeat test, to be performed within 48 hours of the result being available at the site
- The subject's parent(s)/caregiver(s) is/are poorly compliant with study procedures, visits, and assessments, preferably after evaluation and discussion between the investigator and the sponsor
- The randomization code is broken by the investigator or the study-site personnel
- Lost to follow-up
- Sponsor's decision to terminate the study

If a subject discontinues study drug for any reason before the end of the double-blind treatment period, follow-up assessments should be obtained (see TIME AND EVENTS SCHEDULE) before the subject can be withdrawn.

10.4. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- The subject's parent(s)/caregiver(s) is poorly compliant with study procedures, visits, and assessments, preferably after evaluation and discussion between the investigator and the sponsor
- Decision by the sponsor to stop or cancel the study
- Decision by the investigator to withdraw the subject from the study

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

In case subjects prematurely discontinue study drug treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the subject's remaining study visits and assessment schedule, or, at a minimum, to return with the subject to the site for a Withdrawal and a Safety Follow-up Visit. At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed. In case the subject's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase, an optional Withdrawal and Safety Follow-up Visit will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 8 and Day 21 visits, respectively, will be performed.

When a subject's parent(s)/caregiver(s) withdraw(s) the subject before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. If a subject is withdrawn from the study before the end of the double-blind treatment period, every attempt should be made to obtain follow-up assessments (see TIME AND EVENTS SCHEDULE).

10.5. Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

Analyses will be performed on the combined dataset of hospital and outpatient subjects, as well as on data of each cohort separately.

11.1. Interim Analyses

Up to 4 interim analyses are planned (see Figure 2). During and after all interim analyses, investigators, subject(s), and local sponsor representatives (except for selected local sponsor representatives from Japan) will remain blinded. An IDMC will monitor and review data in an unblinded manner, at all interim analyses. Enrollment will continue during each of the interim analyses.

During the first interim analysis, the Sponsor Committee will be unblinded; the central sponsor team members and local sponsor representatives from Japan will remain blinded. For the second interim analysis, the Sponsor Committee, central sponsor team members, and selected local

sponsor representatives from Japan will be unblinded upon recommendation from the IDMC and the Sponsor Committee. During any interim analysis taking place after the second interim analysis, the sponsor, including the central study team, and selected local sponsor representatives from Japan will be unblinded. Aggregate unblinded data and certain individual safety events may be shared with investigators to support the revised risk-benefit evaluation for the current study and to support start of Phase 3.

A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making, considering the IDMC recommendation, and will communicate these decisions to the study team. Details are provided in the IDMC Charter.

The central sponsor team includes the following functions: clinical leader, statistician, virologist, PK leader, pharmacometrician, medical writers, and statistical programmers.

Additional interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities.

Further details regarding the interim analyses will be specified in the SAP. Operating characteristics (power, Type I error, …) of statistical decision procedures and methods at the interim analyses will be evaluated through computer simulations and summarized in a modeling & simulation report.

11.1.1. First Interim Analysis

The first interim analysis encompassing safety and tolerability, PK, and antiviral effect is planned when at least 36 subjects from Cohort 1 have completed the Day 14 assessments (or discontinued earlier). Enrollment in Cohort 1 (including the subcohort) will continue during the interim analysis and IDMC review.

Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 1 (at N 36 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 1 has been randomized.

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 (see also Section 11.12).

11.1.2. Second Interim Analysis

A second interim analysis is planned, 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) have completed the Day 14 assessments (or discontinued earlier). Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily

paused prior to interim analysis 2 (at N approximately 70-80 in Cohort 1), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 1. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 2 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity and one clinical endpoint (ie, time to resolution of symptoms, considering data of both cohorts). In addition, other clinical course and safety-related endpoints will be analyzed. 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 terminate the study for futility, or to terminate the enrollment of the >3 days since symptom onset population. The decision rules will be defined in the SAP.

Depending on enrollment status of Cohort 2, the second interim analysis will not be performed, if it is later than or too close to the predicted timing of the planned third interim analysis.

11.1.3. Third Interim Analysis

A third interim analysis is planned, preferably at the end of a hemispheric RSV season, when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments (or discontinued earlier) and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 3 (at N approximately 70-80 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 3 has been randomized. During this interim analysis, a futility and population enrichment analysis will be performed on antiviral activity (data from both cohorts combined) and clinical endpoints (Cohort 2 data only). The rules implement simultaneously a conditional success probability approach (viral load) and a Go-NoGo approach[10] on multiple clinical endpoints. Both the study team and the IDMC will review the results of the interim analysis, and may recommend to the Sponsor Committee an early termination of the study for futility or to enrich the population and limit further enrollment to patients with ≤3 days since symptom onset, in case the conditional power on the viral load endpoint is regarded as being too low and/or the success probability of the clinical endpoints is too low. The Sponsor Committee will take a decision considering the recommendation of the study team and the IDMC (see also Section 11.12). The exact criteria of these non-binding decision rules will be defined in the SAP.

No clinical endpoints for Phase 3 have been identified yet and the association between the antiviral effect and clinical course endpoints is not yet established for RSV. A key secondary objective of this Phase 2 study is the evaluation of clinical course endpoints and their dependence on viral load reductions. Results of this Phase 2 study will inform on discussion and selection of clinical course endpoints and guide the design for subsequent Phase 3 studies. Therefore, a sample size re-estimation based on clinical course endpoints (Cohort 2 data only) will be performed during interim analysis 3 and may result in an expansion of Cohort 2. Based on all available data from Cohort 2 at the cut-off for interim analysis 3, one or more clinically relevant and sensitive endpoint(s) will be selected for confirmation. Time to resolution (ie, 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 interim analysis 3 for the endpoint selection and sample size recalculation.

After selection of (a) clinical endpoint(s), the number of subjects in Cohort 2 will be calculated to minimize the conditional "consider"-probability for clinical endpoints (Go-NoGo-approach) at the end of the study assuming a required confidence of 90% (one-sided) to exclude the target value and/or the minimal acceptable value.

Both the study team and the IDMC may recommend to the Sponsor Committee an increase of the sample size for Cohort 2 of the study. The maximum number of subjects in Cohort 2 in the study will not exceed 300.

11.1.4. Fourth Interim Analysis

If the study is extended beyond the initially planned sample size in Cohort 2 for the primary analysis (N 150), a fourth interim analysis will be performed preferably at the end of a hemispheric RSV season, after approximately 150 subjects in Cohort 2 have completed the Day 14 assessments (or discontinued earlier), and will include all available data from Cohort 1 and Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum might be temporarily paused prior to interim analysis 4 (at N approximately 150 in Cohort 2), once the maximum number of subjects are enrolled in the >3 days to ≤5 days since symptom onset stratum in Cohort 2. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be reopened once the last subject required for interim analysis 4 has been randomized. The primary analysis on antiviral activity will be performed during this fourth interim analysis 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 preparations, including regulatory interactions. In addition, the futility and population enrichment analysis will be repeated at this interim analysis. Both the study team and the IDMC will provide their recommendations to the Sponsor Committee, who will decide, taking all recommendations into account.

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 will coincide with the primary analysis. Enrollment in the >3 days to ≤5 days since symptom onset stratum will be stopped once the maximum number of subjects are enrolled in this stratum in both cohorts. Since the number of subjects enrolled in Cohort 2 is the trigger to perform interim analysis 3 and interim analysis 4, enrollment in Cohort 1 in the >3 days to ≤5 days since symptom onset stratum might be stopped, at any time after interim analysis 2, once the maximum number of subjects in this stratum are enrolled for the final analysis.

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.

To account for multiplicity, and to be able to define a robust clinical course endpoint for Phase 3, both unadjusted and adjusted p-values, with appropriate Type I error control, will be presented in the final analysis.

11.2. Subject Information

For all subjects who received at least 1 dose of study drug, descriptive statistics will be provided.

All demographic (eg, age, length, weight, race, gender) and other initial subject characteristics (physical examination [length, body weight, head circumference], medical and surgical history, family history, concomitant diseases, RSV disease characteristics) will be tabulated and analyzed descriptively by treatment group.

11.3. Sample Size Determination

11.3.1. Primary Objective: Establish Antiviral Activity

The basis of the sample size calculation is the antiviral results 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 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 5. Based on Study 53718678RSV1005 results, no discrimination between the proposed doses is expected (ie, E_{max} dose-response shape was observed).

Table 5: 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 (eg, 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≥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 (ie, 20%).

In conclusion, 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).

11.3.2. Key Secondary Objective: Clinical Course Effect

During interim analysis 3 (when approximately 70 to 80 subjects from Cohort 2 have completed the Day 14 assessments [or discontinued earlier]; see Section 11.1.3), 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 interim analysis, one or more clinically relevant and sensitive endpoint(s) will be selected for confirmation in the final analysis. Time to resolution (ie, 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 interim analysis 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 "consider"-probability for clinical endpoints (Go-NoGo-approach) at the end of the study, assuming a required confidence of 90% (1-sided) to exclude the target value and/or the minimal acceptable value.

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 (ie, ratio of 66%), and a scale parameter of 1/0.65, a sample size of 48 subjects per treatment arm will reach 95% probability to reach an observed effect in the right direction; based on estimates derived from an accelerated failure time model. This will allow the evaluation of clinical course endpoints in the hospital population compared to the outpatients.

11.4. Efficacy Analyses

The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized subjects who received at least one dose of study treatment and who have a centrally confirmed RSV viral load of ≥1 $\log_{10}$ copies/mL above the LLOQ at baseline.

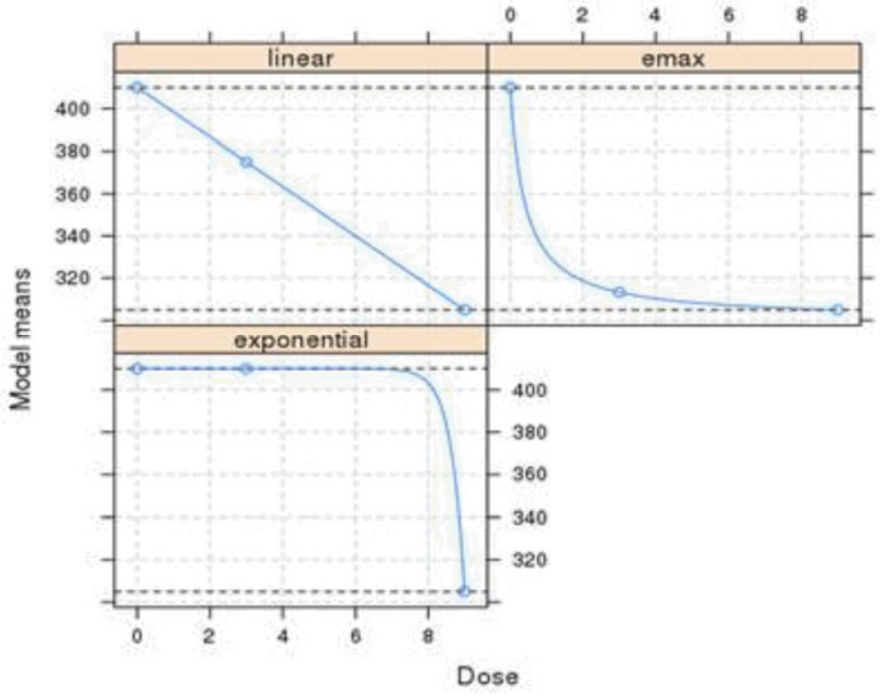
11.4.1. Antiviral Effect

11.4.1.1. Primary Endpoint

The primary objective is to establish antiviral activity of JNJ-53718678. The primary efficacy endpoint is the RSV viral load area under the curve (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. 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. Refer to Section 2.1.

A set of 3 candidate models will be used to cover a suitable range of possible dose-response shapes (linear, E_{max}, exponential) (see Figure 3). Doses of the different age groups will be pooled and transformed to the total daily dose of the oldest age group: low dose (3 mg/kg), high dose (9 mg/kg), and placebo (0 mg/kg) and these will be used for the "treatment groups" in the analysis.

Figure 3: Candidate Models for RSV Viral Load AUC From Baseline Until Day 5



AUC values with corresponding covariance matrix will be determined by modeling the $\log_{10}$ viral load values over time using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within subject errors over time. The Kenward-Roger method will be used to approximate the degrees of freedom.

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 the Type I error rate. A dose-response trend is established when the maximum of the *t*-test statistics exceeds the critical value.

Details will be provided in the SAP that will be finalized before the first formal interim analysis.

11.4.1.2. Secondary Endpoints

The other antiviral endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented. Kaplan-Meier Curves will be produced to graphically describe the time to event data.

Differences between treatment groups in viral load will be derived from the same model as for the primary endpoint using appropriate contrasts deriving least square mean differences, including the 95% 2-sided CIs. Other covariates as well as interaction effects might also be investigated.

The time to undetectable RSV viral load will be analyzed using Kaplan-Meier plots and will be modeled using an accelerated failure time model, adjusted for covariates, such as strata and baseline viral load, to estimate differences between treatment groups. A generalized MCP-Mod approach will be used to test for existence of dose-response, if applicable. For the MCP-Mod approach, doses of the different age groups will be pooled and transformed to the total daily dose of the oldest age group: low dose (3 mg/kg), high dose (9 mg/kg), and placebo (0 mg/kg) and these will be used for the "treatment groups" in the analysis.

More details regarding the analysis of these data will be described in the SAP.

11.4.2. Clinical Course of RSV Infection

All endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented.

Time to-variables (eg, time to resolution of symptoms, time to clinical stability, length of hospital stay) will be analyzed using Kaplan-Meier plots and will be modeled using an accelerated failure time model, adjusted for covariates, such as strata and baseline viral load, to estimate differences between treatment groups. 80% and 95% 2-sided CIs will be calculated. A generalized MCP-Mod approach defined as in Section 11.4.1.1 will be used to test for existence of dose-response.

Parent(s)/caregiver(s) PRESORS and clinician PRESORS scores will be descriptively summarized by treatment group and compared between treatment groups. 80% and 95% 2-sided CIs will be calculated. A generalized MCP-Mod approach as defined in Section 11.4.1.1 will be used to test for existence of dose-response on parent(s)/caregiver(s) PRESORS and clinician PRESORS scores. For the MCP-Mod approach, doses of the different age groups will be pooled and transformed to the total daily dose of the oldest age group: low dose (3 mg/kg), high dose (9 mg/kg), and placebo (0 mg/kg) and these will be used for the "treatment groups" in the analysis.

Clinical course endpoints will be evaluated in Cohort 1 and Cohort 2 separately and will be compared between the 2 cohorts.

More details regarding the analysis of these data will be described in the SAP.

11.4.3. Correlation Between Antiviral Effect and Clinical Course Endpoints

Selected antiviral effect and clinical course endpoints (parent[s]/caregiver[s] PRESORS and clinician PRESORS scores) will be subjected to correlation analysis. Various approaches, including graphical analysis, regression methods but also longitudinal analyses will be utilized.

More details regarding the analysis of these data will be described in the SAP.

11.4.4. Viral Sequencing

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

11.5. Safety Analyses

Safety data will be presented descriptively. Statistical testing of safety data, if appropriate, may be presented in a separate report.

For safety, baseline is defined as the last assessment prior to the first intake of study drug.

The population for the safety analysis will consist of all randomized subjects who received at least 1 dose of study drug.

Adverse Events

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

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

Clinical Laboratory Tests

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

The laboratory abnormalities will be determined per the criteria specified in the DMID (see Attachment 1) pediatric toxicity tables and in accordance with the normal ranges of the clinical laboratory if no gradings were available.

Results from the central laboratory will be included in summary tables. Local laboratory results (in case of cardiac events potentially related to QT prolongation) will be listed only.

Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values at each selected timepoint (the screening ECG will be used as baseline). Frequency tabulations of the abnormalities will be generated.

The ECG variables that will be presented are heart rate, PR interval, QRS interval, QT interval, QTcF, and QTcB.

The percentage of subjects with abnormalities will be tabulated.

Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Vital Signs

Descriptive statistics of body temperature, heart rate, respiratory rate, SBP, DBP, and SpO_2 values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically relevant limits (as defined in the SAP) will be summarized.

Physical Examination

Physical examination findings will be summarized at each scheduled time point.

11.6. Pharmacokinetic Analyses

Population PK analysis of concentration-time data of JNJ-53718678 may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-53718678 and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

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

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

For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of JNJ-53718678, and, if applicable, of metabolites and/or endogenous markers.

11.7. Pharmacokinetic/Pharmacodynamic Relationships

Relationships of JNJ-53718678 population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored. These relationships will be presented in a tabular and/or graphical display.

Results of PK/PD analyses may be presented in a separate report.

11.8. Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group.

11.9. Acceptability and Palatability

Data on acceptability and palatability of the JNJ-53718678 formulation will be presented descriptively.

11.10. Biomarker Analyses

Analyses may be performed at the sponsor's discretion and reported separately from this study. Statistical approaches to explore correlations between clinical outcome, viral load, and biomarkers in blood and mid-turbinate nasal swabs vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences among study subjects.

11.11. Other Analyses

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

11.12. Independent Data Monitoring Committee

An IDMC will be established to monitor and review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review safety data, safety and PK data of the subcohort of Cohort 1 and results from interim analyses. In addition, an IDMC analysis of the safety and PK data of the full cohort of hospitalized subjects (including the full subcohort) is planned after all subjects of Cohort 1 have completed the study (or discontinued earlier). In case the timing of this IDMC analysis coincides with that of one of the scheduled interim analyses, it may be performed as part of that interim analysis. After the review, the IDMC will provide recommendations to the Sponsor Committee.

At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or to the safety assessments to the Sponsor Committee to ensure the safety of enrolled subjects. The IDMC can recommend to the Sponsor Committee to halt a dose arm due to safety concerns.

The IDMC will consist of at least one pediatrician, at least one medical expert in infectious diseases, and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC Charter.

Given the challenges of ensuring study site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the following changes will be considered based on the results of any formal interim analysis and may be modified by recommendation of the IDMC based on the review of this study and data from other ongoing studies: changes with respect to the time since onset of symptoms and changes with respect to dose selection. If the IDMC determines that subjects with a time since onset of RSV

symptoms of 5 days prior to randomization may not achieve benefit based on interim results, they may recommend that the time of onset of RSV symptoms to the time of randomization is reduced. Furthermore, if the IDMC determines that subjects with a time since onset of RSV symptoms longer than 5 days prior to randomization may achieve benefit, this duration may be increased to up to 7 days (ie, 7 days from symptom onset to randomization). In addition, the requirement that a minimum of 45% of all enrolled subjects in Cohorts 1 and 2 (ie, maximum 55% of subjects can be enrolled in the >3 days to ≤5 days stratum) are to have a symptom onset of ≤3 days before randomization, might be modified based on the recommendation of the IDMC after review of the interim data. Also, in case the data shows no viral and clinical benefit on the low dose, the IDMC might recommend to drop the low dose and continue with a 2:1 randomization for high dose versus placebo. If such modifications are recommended by the IDMC and endorsed by the Sponsor Committee, these changes will be communicated in writing to investigators, health authorities, and IEC/IRB and may be implemented without amendment to this protocol. Details are provided in the IDMC Charter.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject's parent(s)/caregiver(s) is the preferred method to inquire about AE occurrence.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-53718678, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.3.1, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

An assessment of severity grade, as per DMID (see Attachment 1), will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Anticipated events will be recorded and reported as described in Attachment 3. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

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

Information regarding serious adverse events will be transmitted to the sponsor using the SAE Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically.

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be

considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

JNJ-53718678 supplied for this study is formulated as a powder for oral suspension containing 1,636 mg/bottle of JNJ-53718678-ZCL. After reconstitution with the appropriate volume of solvent, the final oral suspension is obtained containing 23 mg/mL JNJ-53718678-ZCL (hemi (L)-tartrate salt form), hydroxypropylmethyl cellulose (2910 5 mPa.s), d-a-tocopheryl polyethylene glycol-1000 succinate, sucralose, strawberry flavor, sodium methylparaben, sodium

ethylparaben, hydrochloric acid, simethicone, and purified water. 23 mg/mL of JNJ-53718678-ZCL is equivalent to 20 mg/mL of JNJ-53718678-AAA and 3 mg/mL tartaric acid. The pH of the suspension is >3. Refer to the IB additional information on the formulation.

The JNJ‑53718678 placebo powder for oral suspension is supplied as a 4,068-mg/bottle microcrystalline cellulose and will be reconstituted with an appropriate volume of placebo solvent to obtain a placebo oral suspension.

All study dugs will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

Packaging of study drugs will be done under the responsibility of the sponsor; the clinical release will be performed by the sponsor.

JNJ-53718678 powder for oral suspension, placebo powder for oral suspension and solvent will be packed in amber glass bottles containing all study drugs needed for the described dose schedule. Reconstitution is performed by the study-site pharmacist or study-site staff prior to administration, as described in the pharmacy manual.

Packaging and labeling of JNJ-53718678 and placebo powder for oral suspension will be done in a double-blind way. The pharmacist, study site staff or parent(s)/caregiver(s) will draw the assigned volume from the blinded bottles into the oral dispenser prior to administration to the subject.

Primary packaging will be child resistant (child resistant screw cap on bottle) to accommodate outpatient use.

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

14.3. Labeling

Labeling of study drugs will be done under the responsibility of the sponsor. Study drug labels will contain information to meet the applicable regulatory requirements. No study drugs can be re-labelled without prior approval from the sponsor.

14.4. Handling, and Storage

All study drug should be stored on site and at home as instructed on the label. Refer to the IPPI for additional guidance on study drug handling and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject's parent(s)/caregiver(s), and the return of study drug (if applicable), must be documented on the drug accountability form. The subject's parent(s)/caregiver(s) must be instructed to return all original

containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions.

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- JNJ-53718678 IB and any addenda
- IWRS Manual
- eCRF completion guidelines
- Laboratory manual
- Electronic device for clinician and parent/caregiver PRESORS, logs and tolerability questionnaire
- Completion guides for clinician and parent/caregiver PRESORS, logs and tolerability questionnaire
- Study information and instruction sheets for parent(s)/caregivers(s) regarding study procedures ie, dosing and nasal swabbing
- Specimen collection kits for PK, safety blood and urine samples as well as nasal swab samples
- Contact information page(s)
- Pharmacy manual, including study drug preparation and dispensing instructions
- Oral dosing syringes
- ECG machine and manual

- Additional ancillary equipment, as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

The total blood volume to be collected is considered to be in line with generally acceptable guidelines for the collection of blood samples for this age group.[12] The maximum amount of blood drawn from each subject for study-specific purposes will not exceed 9.2 mL over the duration of the study. In addition, investigational staff should take the customary measures to ensure that study-specific assessments such as blood sampling or nasal swabbing are performed with as little as possible additional stress for the subject. Use of local anesthetics at the spot of the puncture is allowed.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of

study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

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

16.2.3. Informed Consent

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

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

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

If the subject's legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject's legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

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

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

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

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-53718678, to understand

RSV infection, to understand differential drug responders, and to develop tests/assays related to JNJ-53718678 and RSV infection. The research may begin at any time during the study or the post-study storage period. No human genetic testing will be performed on these samples.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. The subject's legally acceptable representative may withdraw their consent for their samples to be stored for research (refer to Section 10.5, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

The doses or treatment regimen of JNJ-53718678 may be modified by recommendation of the IDMC and Sponsor Committee decision at any time for PK, efficacy, or safety reasons based on the review of this and other ongoing studies of JNJ-53718678. If such modifications are recommended based on IDMC review, these changes will be communicated in writing to investigators, health authorities, and ethics committees and may be implemented without amendment to this clinical trial protocol.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

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

- History of passive smoking all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes),
- Details of physical examination at screening

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

- Clinician PRESORS and parent(s)/caregiver(s) PRESORS, medication, nasal swabs, and temperature logs, and the study medication tolerability assessment.

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

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

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the

electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Pediatric RSV Electronic Severity and Outcomes Rating Scales

Pediatric RSV Electronic Severity and Outcomes Rating Scales will be completed by clinician (clinician PRESORS; Attachment 4) and parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS; Attachment 5), respectively, on an electronic instrument provided at the study-site. Responses provided will be recorded directly in the electronic database.

17.6.1. Clinician

The clinician will provide information about the subject's status, symptoms, and behavior on an electronic device at time points noted in the TIME AND EVENTS SCHEDULE. Before completing the first assessment of any subject in the study, the clinician must complete the assigned electronic clinician PRESORS training. Practical training on the electronic device will be available on demand.

17.6.2. Parent(s)/caregiver(s)

The subject's parent(s) or caregiver(s) with routine and frequent experience in caring for the subject will provide information about the subject's status, symptoms, and behaviors as well as the impact of the subject's RSV disease on the household on an electronic device at time points noted in the TIME AND EVENTS SCHEDULE. In addition, for the outpatients (Cohort 2) and subjects after hospital discharge (Cohort 1), the parent(s)/caregiver(s) will record study drug administered, temperature and (home) nasal swab collection on the electronic device in the medication, temperature and nasal swab logs, respectively. All parent(s)/caregiver(s) assessments and logs will be provided in the native language of the parent(s)/caregiver(s). The electronic device will include instructions and training that will be completed upon first use by the parent(s)/caregiver(s) and will be available on demand thereafter if parent(s)/caregiver(s) chooses this option.

17.7. Data Quality Assurance/Quality Control

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

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

17.8. Record Retention

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

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

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

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

17.9. Monitoring

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

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

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

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

17.10.2. Study Termination

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

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

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

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

17.11. On-Site Audits

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

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

17.12. Use of Information and Publication

All information, including but not limited to information regarding JNJ-53718678 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-53718678, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and

contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

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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[23]

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN Upper Limit of Normal	LLN Lower Limit of Normal
Rx 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 **Note: ULN are the adult ULN**				
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
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	----	Gross hematuria

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(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: Cardiovascular Safety – Abnormalities

Electrocardiogram

All important abnormalities from the ECG readings will be listed.

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

Vital Signs

Normal ranges:

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

The following clinically relevant abnormalities, measured at rest, will be defined for vital signs:

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

References:

http://www.pinterest.com/pin/396316835929288711/
http://www.docstoc.com/docs/88983719/Pediatric-Vital-Signs
http://www.coheadquarters.com/PennLibr/MyPhysiology/Appendix/AppendVital1.htm

Attachment 3: Anticipated Events

Anticipated Event

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

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

- Cyanosis
- Pneumonia
- Bronchiolitis
- Respiratory failure
- Rhinitis
- Co-infections (bacterial or viral)

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Safety Assessment Committee

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded Safety Assessment Committee.

Statistical Analysis

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

Attachment 4: Clinician PRESORS v7 (24 May 2018)

CCI

[redacted]

CCI

[redacted]

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[redacted]

CCI

Attachment 5: Parent(s)/Caregiver(s) PRESORS v7.1 (9 July 2018)

CCI

[redacted]

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[redacted]

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[redacted]

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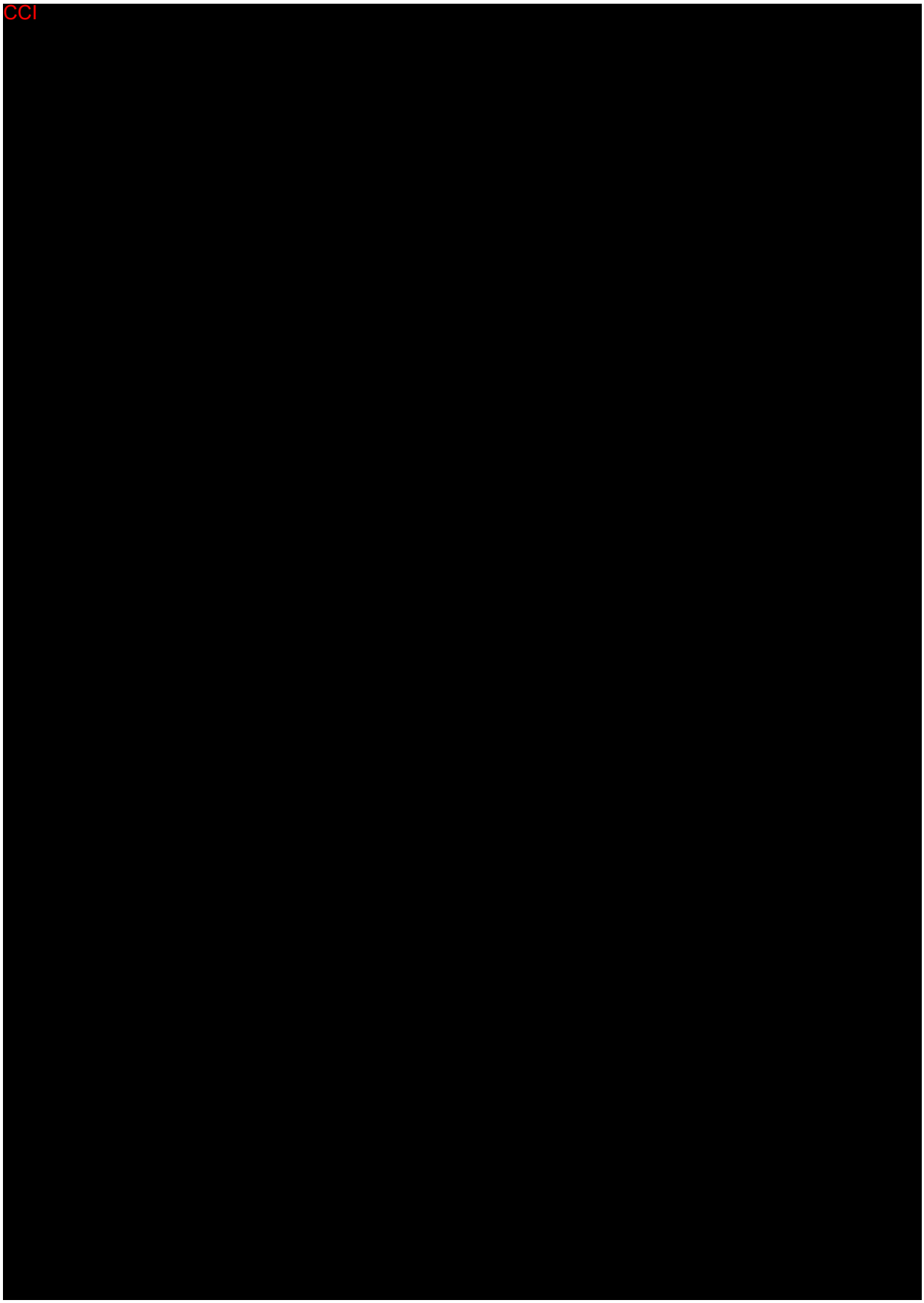

CCI

[redacted]

CCI

[redacted]

Attachment 6: Study Medication Log

Screen Number	Question Text	Response Values
MedLog010	REMINDER: If you have not taken the nasal swab sample from the child today and recorded it in the diary, please do so now, if possible, before giving the study medication.	
MedLog020	Has the child taken the Study Medication today?	Yes 1 No 0
MedLog051	What was the volume administrated?	**Show Labels:** **00.0 mL**
MedLog052	How much of the drug did the child swallow?	All the of the study drug =1 Some of the study drug =2 None of the study drug =3
MedLog053	Did the child vomit or regurgitate the study drug?	Yes =1 No =2
MedLog054	Please inform your study doctor during your next visit exactly how much study medication the child took on this day and the reason why the full dose was not taken. Thank you.	
MedLog050	Please give the child the Study Medication now, and tap Next to confirm.	
MedLog060	Enter the time the child took the Study Medication.	**Show Labels:** false **Min:** 12:00 AM
MedLog070	Please confirm the following information: Time: %d	
MedLog080	What was the main reason you did not give the medication as scheduled?	Nurse or doctor told me to stop giving study medication 1 Forgot to give study medication 2 Study medication was not available 3 Other 4
AFFIDAVIT	Thank you. You have provided all required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.	–

Attachment 7: Nasal Swab Log

Screen Number	Question Text	Response Values
Swab010	Have you collected the nasal swab from the child yesterday?	Yes 1 No 0
Swab020	Please indicate from which nostril the nasal swab was collected yesterday.	Right 1 Left 2
Swab030	At what time the nasal swab was collected yesterday?	**Show Labels:** false **Min:** 12:00 AM
Swab040	Would you like to report a nasal swab collection today?	Yes 1 No 0
Swab060	Please confirm who collected the swab.	Parent/caregiver 1 Health Care Professional 2
Swab050	Please indicate from which nostril the nasal swab is collected today.	Right 1 Left 2
Swab070	At what time was the nasal swab collected today?	**Show Labels:** true **Min:** 12:00 AM
Swab080	Please confirm the following information: Nostril: %n Time: %d	
Swab090	Was the nasal swab placed in the refrigerator?	Yes=1 No=0
AFFIDAVIT	Thank you. You have provided all required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.	–

Attachment 8: Temperature Log

Screen Number	Question Text	Response Values
TempLog010	Have you taken the child's temperature this morning?	Yes 1 No 0
tbc	Have you taken the child's temperature this evening?	Yes 1 No 0
tbc	Have you taken the child's temperature today?	Yes 1 No 0
TempLog020	Please take the child temperature now, and tap next to confirm.	
TempLog030	Enter the time you took the temperature.	**Show Labels:** false **Min:** 12:00 AM
TempLog040	What was the temperature? Celsius	**DefaultVal:** 37 **Min:** 34 **Max:** 41 **Step:** 0.1 **Precision:** 1
TempLog041	What was the temperature? Fahrenheit	**DefaultVal: 98** **Min:** 94 **Max:** 105 **Step:** 0.1 **Precision:** 1
TempLog050	Please confirm the following information: Temperature: %t Time: %d	
	Did you give the child any medicine to reduce fever within the last 4 hours before taking the child's temperature?	Yes 1 No 0
AFFIDAVIT	Thank you. You have provided all required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.	–

[Morning and evening question to be asked through D14, today questions to be asked D15-20]

Attachment 9: Study Medication Tolerability Assessment

Study Medication Tolerability – Caregiver Assessment

[NOTE: Text in bold explains which questions are asked when and to guide implementation on the eDevice in this protocol; they do not need to be translated.]
This tolerability assessment is used in pediatric clinical treatment trials. It is to be administered at the time point specified in the study protocol Time and Events Schedule. For studies using electronic COA assessments, this assessment should also be included in the eCOA implementation.

In general, how did the child react when he/she was given the medicine? (note all that apply)

- ☐ Child took medicine easily ***[cannot be checked if other options selected]***
- ☐ Disgusted expressions after tasting medicine
- ☐ Cried after tasting medicine
- ☐ Would not open mouth or turned head away to avoid medicine
- ☐ Spit out or coughed out medicine
- ☐ Gagged
- ☐ Vomited (within 2 minutes of swallowing medicine)

Thank you!

Attachment 10: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor will be providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects' parents/caregivers will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects' parents/caregivers will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subjects' parent(s)/caregiver(s) and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- These emergency provisions are meant to ensure subject safety on study while site capabilities are compromised by COVID-19 related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, the original protocol procedures should take preference.
- Virtual visits, missed assessments/visits and out-of-window visits will be labelled with the prefix "COVID-19-related" in the eCRF/eSource by the site personnel where needed.
- Administration of the study intervention:

  If a subject cannot visit the site in person for the first administration of study intervention (Day 1), trained delegated staff, in accordance with local regulations, can visit subject's home to:

  - instruct subjects' parent(s)/caregiver(s) on how to use and store the study drug for at-home dosing as per sponsor dosing instructions.
  - administer the first study intervention themselves or supervise the subjects' parent/caregiver during first study intervention administration.
  - monitor any AEs related to dosing.

  The date and time of the study intervention administration at the subject's home at Day 1 will be documented in the subject's source documents and in the eCRF.
- Subject Visits/Assessments:

  If a subject cannot visit the study site in person at Day 1, the sponsor recommends that any study assessment that may be captured during home visit (such as but not limited to ECG, mid turbinate nasal swab, PK blood sample collection, Clinician PRESORS and clinical evaluation) for that particular visit be collected. These assessments and collection should be performed at subject's home by trained delegated site staff or home health service staff.

  If required, mid turbinate nasal swab and PK samples collection can be stored and picked up by site staff or courier. In that case, provision of dry ice is required for PK blood samples.

  There are some assessments that could be conducted virtually via telephone (or videoconference, eg, Facetime, Skype, if possible) with subjects' parent(s) /caregiver(s) in their homes. This methodology can only be used in accordance with applicable (including local) laws, regulations, guidelines and procedures. These virtual assessments include review of AEs, concomitant medications, monitoring of parent(s)/caregiver(s) PRESORS completion and medical resource utilization. Please note, the visit windows included in the TIME AND EVENTS SCHEDULE are still applicable. It must be documented in the eCRF and in the subjects' source documents when a visit occurs virtually due to COVID-19.

  The study assessments that require investigator judgement should be conducted by a qualified site member identified on the site delegation log.
- In case home visits cannot be performed (either due to institute policy or due to local regulations), such study assessments that can be performed virtually are accepted.

- On-site Monitoring visits:

  In case on-site monitoring visits are not be possible due to local regulations, restrictions and guidance, the Site Manager will conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in future to catch up on source data verification. Remote source data verification of electronic records might be performed if possible and if allowed by local/national regulations, restrictions and guidance.

- During the COVID-19 pandemic and at the impacted sites, clinical Site GCP Audits with direct impact/engagement from the clinical investigator team would be not conducted to comply with national, local and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.
- When, per local procedures, both caregivers need to provide consent, the sponsor allows obtaining the second consent remotely (phone or video) if allowed per local guidance.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: Janssen Research & Development

Signature: _____ Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	01-Dec-2020 15:25:28 (GMT)	Document Approval