Janssen Research & Development *

A Two-Part Study With a Birth Cohort (Observational Stage) for Early Diagnosis of Respiratory Syncytial Virus (RSV), Followed by an Optional Phase 2a, Randomized, Double-blind, Placebo-controlled Study (Interventional Stage) to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of JNJ-53718678 in Infants With Acute Respiratory Tract Infection due to RSV

Protocol 53718678RSV2006; Phase 2a

AMENDMENT 3

JNJ-53718678

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2019-001509-25

Status: Approved
Date: 13 July 2020
Prepared by: Janssen Research & Development
EDMS number: EDMS-ERI-182253307, 13.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	13-Jul-2020
Amendment 2	05-Jun-2020
Amendment 1	06-Nov-2019
Original Protocol	23-May-2019

Amendment 3 (13 July 2020)

The overall reason for the Amendment: The overall reason is to implement recommendations from Health Authorities (HA).

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 2.3.5 Benefit-Risk Assessment for Study Participation	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.	Given that potential QT prolongation is C_{max} related, as observed in the TQT study 53718678RSV1009, timing of the ECG is more specifically aligned with the timing of expected C_{max} both after the first dose and at steady state, in line with recommendations by HA.
7.1 Discontinuation of Study Intervention 8.4.3 Electrocardiograms 8.5 Specific Toxicities and Safety Topics of Special Interest	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.
2.3.5 Benefit-Risk Assessment for Study Participation 6.5 Concomitant Therapy	The BCRP inhibitors eltrombopag and curcumin were added to the disallowed concomitant therapies.	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.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 8.2.2 Double-blind Treatment Phase 8.8 Pharmacokinetics	Flexibility was added in the protocol with regard to the day of the specific PK samples to be collected at least 4 hours after the AM and prior to the PM dosing, ie, either on Day 3 or Day 5.	Provide additional flexibility in the protocol with regard 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.
6.5 Concomitant Therapy	Removal of azithromycin as generally allowed medication.	Correction to an oversight of the previous amendment related to disallowed concomitant medications with QT-prolonging effects. Azithromycin is a QT prolonging drug allowed with restrictions.
Throughout	Minor corrections and clarifications were done throughout.	

Amendment 2 (05 June 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to implement a risk mitigation plan for the newly recruited participants in the interventional stage following identification of an exposure (C_{max})-related important potential risk of QT interval prolongation identified in the TQT Study 53718678RSV1009 in healthy adult participants.

Section Number and Name	Description of Change	Brief Rationale
2.2 Background 2.3.4 Potential Risks for Study Participation 2.3.5 Benefit-Risk Assessment for Study Participation	The important potential risk of QT interval prolongation identified in the TQT study was added.	A new important potential risk of QT interval prolongation was identified from the above-mentioned TQT study and this was reflected in relevant sections of the protocol.
2.2 Background 2.3.4 Potential Risks for Study Participation 2.3.5 Benefit-Risk Assessment for Study Participation 11 REFERENCES	Recently available relevant clinical data were included in the introduction. Accordingly, the Investigator's Brochure Addendum to Edition 06 was added as a reference.	Newly available clinical data are reflected in the relevant sections of the protocol.
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 4.1 Overall Design 4.3 Justification for Dose 6.1 Study Interventions Administered 8.2.2 Double-blind Treatment Phase 8.7 Treatment of Overdose	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 definitions of missing dose and overdose were adapted accordingly.	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.
6.5 Concomitant Therapy	Moderate CYP3A4 inhibitors were added to the disallowed prescription medications 14 days prior to screening until 3 days after the last study intervention dose (in addition to the already disallowed strong CYP3A4 inhibitors). The period for strong CYP3A4 inhibitors being disallowed was aligned with that for moderate ones, ie, to 3 days after last study intervention intake.	The increase of C_{max} due to CYP3A4 inhibition needs to be avoided in view of the QT interval prolongation risk to maintain the safety margin. Given that the $t_{1/2}$ of JNJ-53718678 is approximately 10 hours, study intervention is washed out after 3 days.
6.5 Concomitant Therapy	Medications with a known risk to prolong the QT interval cannot be initiated at screening and/or during the study intervention treatment period.	Part of QT prolongation mitigation measures to ensure participants' safety.
2.3.5 Benefit-Risk Assessment for Study Participation	Close monitoring of the use of concomitant medications to be conducted regularly was added.	Part of QT prolongation mitigation measures to ensure participants' safety.
7.1 Discontinuation of Study Intervention 8.4.3 Electrocardiograms 8.5 Specific Toxicities and Safety Topics of Special Interest	A study intervention discontinuation and withdrawal criterion specific to QT interval changes to values >500 ms on ECG was added.	Part of QT prolongation mitigation measures to ensure participants' safety.
1.3 Schedule of Activities	The frequency of ECG monitoring was	Enhancement of the cardiac-related

Section Number and Name	Description of Change	Brief Rationale
(SoA)	increased by adding measurements at Day 1 (1 hour post the first dose) and Day 3 of the interventional stage.	safety follow-up. Part of QT prolongation mitigation measures to ensure participants' safety.
5.2 Exclusion Criteria 8.4.3 Electrocardiograms	Several exclusion criteria related to cardiac safety were added. Exclusion criterion 8 was made more stringent (ie, confirmed QTcF interval >450 ms).	Part of QT prolongation mitigation measures to ensure participants' safety.
1.3 Schedule of Activities (SoA) 2.3.5 Benefit-Risk Assessment for Study Participation 9.3.4 Safety Analyses 10.2 Appendix 2: Clinical Laboratory Tests	A safety measure regarding hypokalemia and hypomagnesemia was added.	Part of QT prolongation mitigation measures to ensure participants' safety.
8.5 Specific Toxicities and Safety Topics of Special Interest 10.8 Appendix 8: Visit Schedule for Rash Management in Pediatric Participants	The specific Rash Management section and corresponding Appendix were removed.	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.
8.5 Specific Toxicities and Safety Topics of Special Interest 9.3.4 Safety Analyses	Specific toxicity management for cardiac events potentially related to QT prolongation was added.	Part of QT prolongation mitigation measures to ensure participants' safety.
1.3 Schedule of Activities (SoA) 4.1 Overall Design 5.1 Inclusion Criteria 5.2 Exclusion Criteria 7.2 Participant Discontinuation/Withdrawal From the Study 8.1.2 Diagnostic Phase 10.7 Appendix 7: Guidance on Study Conduct During the COVID-19 Pandemic	COVID-19-related measures were added.	Added to avoid (co)-infection with SARS-COV-2 as this would confound symptom evaluation during the post-diagnostic phase as well as evaluation of the clinical course of RSV. These measures provide guidance on study conduct during the COVID-19 pandemic.
1.1 Synopsis 4.1 Overall Design 5 STUDY POPULATION 9.1 Sample Size Determination	The maximum sample size of the birth cohort was increased to 1,300 participants.	As the start of the study was late in the RSV season in Panama where the majority of the birth cohort was recruited, a relatively low number of participants were recruited in the interventional stage. The RSV season and opportunity to enroll in the interventional stage were missed in Argentina and Taiwan due to the temporary hold of the interventional stage. To ensure that the target of 40 participants in this stage is achieved, the maximum sample size of the birth cohort was increased.
1.3 Schedule of Activities (SoA)	Systolic and diastolic blood pressure assessment was added to the RSV-like ARI	Assessment was inadvertently missing from the Schedule of

Section Number and Name	Description of Change	Brief Rationale
	visit.	Activities. Alignment with the eCRF.
1.1 Synopsis 1.3 Schedule of Activities (SoA) 8 STUDY ASSESSMENTS AND PROCEDURES 8.2.2 Double-blind Treatment Phase 8.8 Pharmacokinetics	PK sample on Day 1 approximately 1 hour postdose (approximately at C_{max}) and after ECG measurement was added. The timing of the Day 3 sample was adjusted to at least 4 hours after the AM and prior to the PM dosing on Day 3.	Changes in PK schedule 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. Part of risk mitigation plan to ensure participants' safety.
10.5 Appendix 5: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007, draft)	A clarification was added (ULN are adult ULN) to the creatinine values of participants older than 3 months of age in Attachment 1 (DMID Pediatric Toxicity Tables).	For clarification based on feedback from the DMID Authors.
8.6 Adverse Events and Serious Adverse Events 8.6.3 Regulatory Reporting Requirements for Serious Adverse Events 10.2 Appendix 2: Anticipated Events	Reference to anticipated events in the applicable sections of the protocol and the Anticipated Events Appendix were removed.	Anticipated events are included for studies conducted at US sites due to specific FDA guidance on adverse event reporting. This study is not conducted in the US.
1.1 Synopsis 9.4 Interim Analysis	A statement was added that interim analyses may be performed at the sponsor's discretion.	To allow for interim analyses to support decision making for further development of JNJ-53718678 and to support interactions with Health Authorities.
8 STUDY ASSESSMENTS AND PROCEDURES	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.
1.1 Synopsis 4.1 Overall Design 4.4 End of Study Definition	The sentence "For RSV(-) participants who consented to the stool sample collection, the study ends either when the most relevant RSV surveillance data indicate that RSV is out of circulation or on the day of stool sample collection at the participant's age of 4 months (±2 weeks), whichever is last." was added.	Added for clarification.
1.3 Schedule of Activities (SoA) 8.1.2 Diagnostic Phase	Text was added, that if the diagnostic nasal mid-turbinate sample during the RSV-like ARI visit is taken within 4 hours from the sample for testing at home, the nasal mid-turbinate swab sample during the RSV-like ARI visit should be taken from the other nostril. In that case nasal mid-turbinate swab samples should be continued to be collected from the same nostril as used during the RSV-like ARI visit.	Added for clarification.
1.3 Schedule of Activities (SoA)	Clarification that the optional blood sample for exploratory biomarker analyses will only be collected at the first RSV-like ARI visit.	Added for clarification.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.1.2 Diagnostic Phase 8.1.3 Post-diagnostic Phase	Clarification added that the optional stool sample at 21 days (+2 weeks) after the ARI alert does not need to be collected if this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected.	Clarification to avoid duplicate sampling.
1.3 Schedule of Activities (SoA)	+21 days was added to the stool sample collection at the RSV mobile App alert and the sample at the RSV-like ARI visit was removed.	Clarification that the optional stool sample should be collected at 21 days (+2 weeks) after the ARI alert.
Throughout	Minor corrections and clarifications were made.	

Amendment 1 (06 Nov 2019)

Overall Rationale for the Amendment: The overall reason is to update the protocol to add the missing part of the Visit Schedule for Rash Management in Pediatric Participants in Appendix 8.

Section Number and Name	Description of Change	Brief Rationale
10.8 Appendix 8: Visit Schedule for Rash Management in Pediatric Participants	The protocol was updated to add the missing part of Appendix 8.	To correct for the inadvertent omission of the second part of the visit schedule for rash management (follow-up through Day 8 and further visits) in Appendix 8.
1.3 Schedule of Activities (SoA)	The protocol was updated to add the allowed window (ie, ±3 days) to the end of study visit of the observational stage in the Schedule of Activities.	To align with the protocol text.
4.4 End of Study Definition	The protocol was updated to add a note to clarify that the window allowed for the optional stool sampling is 21 days (+2 weeks) in the post diagnostic stage of the observational stage of the study for RSV positive patients who do not enter the interventional stage of the study.	The allowed window (+2 weeks) for the collection of the optional stool sample is larger than the window (±3 days) of the end of study visit (Day 21) of the observational stage of the study. This longer window is required to ensure collection of a good quality stool sample that is usable for subsequent assessments.
1.3 Schedule of Activities (SoA)	In the Schedule of Activities (Part 1: Observational Stage – RSV(+) Outpatients NOT Enrolled in Interventional Stage; footnote d), the crosslink to Section 8.3.2 was replaced with a crosslink to Section 8.3.1.	To correct crosslinking.
6.1 Study Interventions Administered	The protocol was updated to include the Chemistry, Manufacturing, and Controls (CMC) summary of the administered study intervention.	To provide more information on the study intervention.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Two-Part Study With a Birth Cohort (Observational Stage) for Early Diagnosis of Respiratory Syncytial Virus (RSV), Followed by an Optional Phase 2a, Randomized, Double-blind, Placebo-controlled Study (Interventional Stage) to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of JNJ-53718678 in Infants With Acute Respiratory Tract Infection due to RSV

JNJ-53718678 is an investigational respiratory syncytial virus (RSV) specific fusion inhibitor under development for the treatment of RSV infection.

STUDY RATIONALE

RSV is considered the most important virus causing acute lower respiratory tract infection (LRTI) and a major cause of hospital admissions and death in young children worldwide. Infants born prematurely or close to the RSV circulation and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI. At the time of RSV intercept when the infants are brought in (on the parent/caregiver's initiative) for medical care for an acute respiratory infection (ARI), the RSV viral load is mostly already past its peak and declining, whereas the disease can still evolve. In order to have a significant effect on the disease severity, treatment needs to be started as soon as possible to prevent further replication of the virus and the ensuing inflammatory response leading to the clinical signs/symptoms and to maximize the potential for the study medication to exert its antiviral effects, thereby affecting the clinical course of the disease.

This study is designed to assess in the setting of a planned early interception of pediatric RSV disease, early viral and disease kinetics (observational stage) and the antiviral effects of an RSV fusion inhibitor, JNJ-53718678 (interventional stage). In the observational stage the infant is closely monitored for early symptoms by the parent(s)/caregiver(s) and thus may be brought in for diagnosis earlier than in the typical setting.

To ascertain that children will be recruited with a primary RSV infection at an age where disease severity is significant, parent-child pairs will be recruited when the child is less than 4 months old and born after the end of the season preceding the initiation of the study.

OBJECTIVES AND ENDPOINTS

Objectives

Part 1: Observational Stage

- To evaluate the onset and evolution of clinical symptoms of pediatric RSV disease
- To evaluate the relationship between viral load and clinical symptoms at early diagnosis of pediatric RSV disease

Part 2: Interventional Stage

The primary objective is to evaluate 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 an early intervention setting in infants (≤4 months of age at enrollment) recruited from a birth cohort.

The secondary objectives are to assess:

- the impact of treatment with 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

Endpoints

Part 1: Observational Stage

- the total score, over time, of respiratory symptoms as captured by the RSV mobile Application (App) during the pre-diagnostic phase and the post-diagnostic phase for RSV(+) participants that do not enter in the interventional stage
- the Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS) scores by the clinician (clinician PRESORS) on the day of RSV diagnosis
- RSV viral load kinetics during the pre-diagnostic phase
- RSV viral load kinetics from Day 1 to Day 8 after RSV diagnosis over time (if not participating in the interventional stage)
- the PRESORS scores by parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) over time

Part 2: Interventional Stage

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

Secondary endpoints of the interventional stage can be summarized as follows:[a]

- 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 (start of study medication) over time
  - RSV viral load AUC from immediately prior to first dose of study medication (baseline) through Day 3, Day 8, and Day 14
  - time to undetectable RSV viral load
  - proportion of participants with undetectable RSV viral load at each time point throughout the study
- clinical course related endpoints:
    - the following endpoints will be based on the PRESORS assessed throughout the interventional stage of 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 assessed throughout the study by parent(s)/caregiver(s) PRESORS
      - change from baseline in parent(s)/caregiver(s) PRESORS (worsening or improvement)
      - change from baseline in clinician PRESORS (worsening or improvement)
      - time to resolution (ie, to none or mild) of RSV symptoms

[a] Exploratory objectives and corresponding endpoints are provided in Section 3 of the protocol.

- time to improvement based on general questions on overall health
- proportion of participants with improvement or worsening of RSV disease based on general questions on overall health on each study day from screening till Day 21
- 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 during scheduled visits
- need for (re)hospitalization during treatment and follow-up

- safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), and vital signs, throughout the interventional stage of the study
- PK parameters of JNJ-53718678, as determined by population PK (popPK) modeling

Hypothesis

Part 1: Observational Stage

For the observational stage no formal hypothesis will be tested.

Part 2: Interventional Stage

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV as assessed by a reduction in RSV viral load AUC (from immediately prior to first dose of study medication [baseline] until Day 5) at the 5% level (one-sided) for JNJ-53718678 compared to placebo in participants recruited from a birth cohort.

OVERALL DESIGN

This study is designed to assess the impact of early interception and intervention on antiviral activity and the clinical course of the disease. The study consists of 2 parts: an observational stage with a birth cohort and a Phase 2a, multicenter, randomized, double-blind, placebo-controlled interventional stage.

In the observational pre-diagnostic phase, the study aims to record early signs and symptoms of potential RSV infections and is focused on bringing the infant in for assessment at a threshold score that is based on a combination of at least one sign of upper respiratory infection, any sign of lower respiratory involvement and any sign of systemic impact (eg, feeding difficulty, disturbed sleep, disturbed activity level). All infants will be closely monitored for early signs and symptoms of RSV disease using a mobile RSV App on the parent/caregiver's mobile phone (pre-diagnostic phase). For those infants with scores that cross the threshold score an alert will be sent and they will be brought to the study site for an early diagnostic RSV test (diagnostic phase). RSV(-) participants will return to the pre-diagnostic phase and will be further closely monitored by the parent(s)/caregiver(s) through the RSV mobile App. There will be a 7-day pause in the RSV mobile App for the generation of alerts, after which the alert option will be switched back on. RSV(+) participants will be enrolled in the screening phase of the interventional stage of the study after obtaining informed consent for the interventional stage at that time. RSV(+) participants whose parent(s)/caregiver(s) do not consent for enrollment in the interventional stage and participants who are screening failures in the interventional stage will enter the post-diagnostic phase of the observational stage (hospitalized or outpatients). Upon an alert, if a participant is SARS-CoV-2 positive assessed by local health practice, the participant will be withdrawn from study.

The interventional stage will consist of a screening phase, a treatment phase (hospitalized or outpatients), and a posttreatment follow-up phase. Newly recruited participants will be randomized in a 1:1 ratio to receive either JNJ-53718678 or placebo twice daily (bid) AM and PM for 7 days (14 consecutive doses). For participants 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 participants receive 14 consecutive doses in

total. Antiviral activity, clinical outcomes, safety, tolerability, and PK of JNJ-53718678 in infants at early stage of an ARI due to RSV will be evaluated.

The observational stage involves nasal swabbing for RSV diagnosis, viral assessments (RSV RNA viral load), exploratory biomarker analysis, blood sampling (optional) for exploratory biomarker analyses, stool sampling (optional) for microbiome analysis, buccal swab collection (optional) for exploratory host genetic analyses, and completion of questionnaires (evaluation questionnaires and PRESORS).

In the post-diagnostic phase of the observational stage, for the RSV(+) participants whose parent(s)/caregiver(s) do not consent for enrollment in the interventional stage and participants who are screening failures in the interventional stage, the parent(s)/caregiver(s) will be asked to continue with the twice daily RSV mobile app and to also complete the PRESORS over the same period.

The interventional stage involves nasal swabbing, viral assessments (RSV RNA viral load, RSV subtype determination, and sequencing), blood sampling for PK, and completion of questionnaires (PRESORS).

Study duration will be approximately 29 (±3) days after RSV(+) diagnosis for participants who enter the interventional stage, and 21 (±3) days after RSV(+) diagnosis for participants who do not enter the interventional stage (or 21 days [+2 weeks] in case optional stool samples will be collected [the additional time is only for optional stool sample assessments]). RSV(-) participants will be considered to have completed the study at the end of the RSV circulation. For RSV(-) participants who consented to the stool sample collection, the study ends either when the most relevant RSV surveillance data indicate that RSV is out of circulation or on the day of stool sample collection at the participant's age of 4 months (±2 weeks), whichever is last.

An Independent Data Monitoring Committee (IDMC) will be commissioned for the interventional stage.

NUMBER OF PARTICIPANTS

A target of 1,300 infants (≤4 months of age at enrollment and asymptomatic for ARI-like symptoms requiring medical intervention at the time of consent) is planned to be enrolled globally in the observational stage of this study.

It is anticipated that approximately 40 RSV(+) infants from the observational stage of the study will be enrolled in the interventional stage. Participants should be ≥28 days old (or ≥3 months postnatal age for prematurely born infants) and at least 2.4 kg to be eligible for enrollment in the interventional stage of the study.

The enrollment period for the observational stage will be guided by local RSV epidemiological distribution and dynamics. Start and end of the RSV circulation will be dependent on the respective country/region where the study will be conducted. The determination by the sponsor to end the study will be done on a per-site basis in line with the local seasonality pattern.

INTERVENTION GROUPS AND DURATION

After Amendment 2, newly eligible participants in the interventional stage will be randomized 1:1 to receive either JNJ-53718678 or placebo. Randomization should occur within 32 hours after the receipt of RSV mobile App alert, and will be stratified based on the time between ARI alert and randomization (<24 hours or ≥24 hours). Treatment should start as soon as possible, but within 4 hours after randomization. Study medication will be administered bid for 7 days (14 consecutive doses). For participants 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 participants 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. Doses are based on body weight and age group. Infants ≥28 days and

<3 months of age will receive 2.5 mg/kg bid, infants ≥3 and <6 months of age will receive 3 mg/kg bid, and infants ≥6 months of age will receive 4.5 mg/kg bid (or matching placebo).

EFFICACY EVALUATIONS

Antiviral Activity (Interventional Stage)

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

Clinical Course of RSV Infection

The clinical course of RSV infection will be evaluated for all RSV(+) participants (hospitalized or outpatients) during either the post-diagnostic phase of the observational stage (for those who do not enter the interventional stage or are screen failure in the interventional stage) or the interventional stage of the study, including but not limited to:

- respiratory rate, heart rate, SpO_2, and body temperature as measured by the investigator
- body temperature as measured by the parent(s)/caregiver(s)
- 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 by the investigator (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 disease per investigator assessment
- the need for antibiotics related to complications associated with RSV disease per investigator assessment
- for hospitalized patients only: time to discharge (from initial admission and from initiation of study treatment), time to clinical stability, with clinical stability evaluated by the investigator (from initial admission and from initiation of study treatment), level of and duration by level of hospital care (eg, intensive care unit [ICU], translational care unit, ward floor), oxygen requirement type (eg, supplemental oxygen, noninvasive pressure ventilation, endotracheal-mechanical ventilation), and duration, and hydration and feeding by intravenous (IV) line/nasogastric tube and duration

Viral Sequencing

In the interventional stage, 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 presence of baseline RSV F-gene polymorphisms on the antiviral response will be explored.

SAFETY EVALUATIONS

During the observational stage of the study, all serious and non-serious AEs related to the study sampling procedures and all deaths (including their causality) will be documented from signing of the informed consent form (ICF) allowing inclusion in the observational stage onwards.

Safety and tolerability will be evaluated throughout the interventional stage, ie, from signing of the ICF allowing inclusion in the interventional stage onwards until the last study-related activity, and will include

the following evaluations: AEs, clinical laboratory tests (local), 12-lead ECG, vital signs, and physical examination.

PHARMACOKINETIC EVALUATIONS

For newly recruited participants in the interventional stage, a blood sample for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick approximately 1 hour after administration of study drug (after the ECGs are obtained) on Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

BIOMARKER AND PHARMACOGENOMIC (DNA) EVALUATIONS

Stool samples for microbiome analysis will be optionally collected during the study to assess diversity and relative abundance of bacterial species.

In the observational stage, optional blood samples will be used for exploratory biomarker analyses (eg, proteins, RNA, immune cell populations), on the premise that these analyses investigate the role of biomarkers in RSV-related disease. Leftover mid-turbinate nasal swab samples from samples collected during the study may also be used for exploratory biomarker analyses (eg, proteins, RNA, immune cells, microbiome).

In the observational stage, host genetic variation analysis (DNA) can be performed only on optional samples collected from participants whose parent(s)/caregiver(s) provided informed consent for buccal swab collection and human DNA testing.

STATISTICAL METHODS

Sample Size Determination

The sample size of the interventional stage is based on results obtained in an earlier birth cohort study (Janssen R&D, data on file) and the specified analysis method using simulated data. Based on 10,000 simulated datasets of 40 participants, with an assumed 10% drop-out rate and an effect size of early treatment of 0.75 $\log_{10}$ copies.day/mL reduction in viral load versus placebo on average, there is a power of 88% to reject the null hypothesis of no antiviral effect of JNJ-53718678 treatment using a significance level of 5% (one-sided).

The sample size of the birth cohort is based on the sample size required for the interventional stage. It is assumed based on the results of a previous observational birth cohort study (Janssen R&D, data on file) that approximately 10% of the infants participating in the birth cohort will be diagnosed as RSV(+) and will develop ARI disease signs compatible with a minimum disease severity threshold for intervention.

At the stage of the temporary hold of the interventional stage of the study on 2 March 2020, 862 infants were enrolled in the birth cohort, leading to 29 infants who were diagnosed as RSV(+) and 20 infants who participated in the interventional stage. The incidence of RSV(+) was lower than anticipated, which for a large part may be explained by the relatively late in the RSV season start of recruitment for the first participating country in the study (Panama). It is assumed that when recruitment into the birth cohort is re-initiated in time for the next season, ~10% of participants will be diagnosed as RSV(+). In order to maintain the target of 40 participants in the interventional part, the maximum number of infants that may be recruited in the birth cohort is set at 1,300. With an additional 438 participants in the birth cohort, an assumption of 10% incidence of RSV(+) and a 50% rate of infants who will enter the interventional stage, the target of 40 participants in the interventional stage is expected to be reached.

As the sample size of the 2 parts are linked and assumptions have to be made on the percentages of RSV(+) and eligibility, the study may continue at the discretion of the sponsor when more than 40 participants are included in the interventional part (with a maximum of 60) and may also be considered completed if at least 32 infants have been included in the interventional part.

Viral Kinetics and Clinical Outcome Analyses

Details regarding the analyses will be described in the Statistical Analysis Plan (SAP).

Viral Load Kinetics (Observational Stage)

Viral load kinetics will be determined based on measurements of RSV viral load in nasal secretions by a qRT-PCR assay on mid-turbinate nasal swab specimens. These data will be analyzed descriptively and graphically. For the RSV viral load assessed before the day of RSV diagnosis and at the diagnosis itself it will be investigated if the signs and symptoms observed and captured previous to these RSV viral load assessments have predictive value for the absence or presence of the virus as well as for the key characteristics of the viral load (eg, peak viral load), when virus is present. The correspondence between viral load and signs and symptoms will be investigated graphically by visualizing the viral load and signs and symptoms together over a period of time before and after RSV diagnosis. Exploratory analyses and details will be described in the SAP.

Antiviral Activity (Interventional Stage)

Viral load kinetics will be determined based on measurements of RSV viral load in nasal secretions by a qRT-PCR assay on mid-turbinate nasal swab specimens. These data will be analyzed graphically and descriptively. Kaplan-Meier Curves will be produced to describe the time to event data. The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized participants who received at least one dose of study medication and who have a centrally confirmed RSV infection with an RSV viral load of $\geq$1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) at baseline.

The primary efficacy endpoint is the RSV viral load AUC from immediately prior to first dose of study medication through Day 5 ($AUC_{1\text{-}5\ days}$) derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs. Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, stratum (time from ARI alert within 24 hours or outside 24 hours), 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. Differences between treatment groups in viral load for time points, and the difference in the $AUC_{1\text{-}5\ days}$ between treatment groups will be derived using appropriate contrasts deriving least square mean differences, including the 90% 2-sided confidence intervals. The primary null hypothesis of worse or no treatment effect will be rejected if the viral load $AUC_{1\text{-}5\ days}$ is significantly lower than placebo using a one-sided test at the 0.05 significance level.

Clinical Course of RSV Infection

Endpoints related to evaluation of the clinical course of RSV infection will be analyzed graphically and descriptively. Both scores from the RSV mobile App as well as PRESORS scores will be summarized descriptively over time and may be modeled using longitudinal analysis. Relationship between symptoms reported on the RSV mobile App and becoming RSV(+) (versus RSV[-]), and need for hospitalization (versus outpatient) will be investigated graphically. Also, correlation between symptoms reported on the RSV mobile App as predictive of viral load characteristics will be investigated, as well as correlation between signs and symptoms and viral load over time. Time-to variables will be analyzed using Kaplan-Meier plots. For the interventional stage these might be modeled using an accelerated failure time model, adjusted for covariates, such as stratum and baseline viral load, to estimate differences between treatment groups. Endpoints related to hospital stay will be explored.

Viral Sequencing

Pre-treatment polymorphisms and relevant post-baseline changes in the RSV F-gene (and other regions of the RSV genome, if applicable and on request of the sponsor's virologist) will be tabulated and described. The effect of pre-treatment RSV F-gene polymorphisms and relevant post-baseline RSV F-gene changes on antiviral response and/or clinical outcomes will be explored.

Safety Analyses

All safety data will be summarized descriptively.

Pharmacokinetic Analyses

PK analysis will be performed using a popPK approach by means of nonlinear mixed-effects modeling.

Biomarkers Analyses

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

Interim Analysis

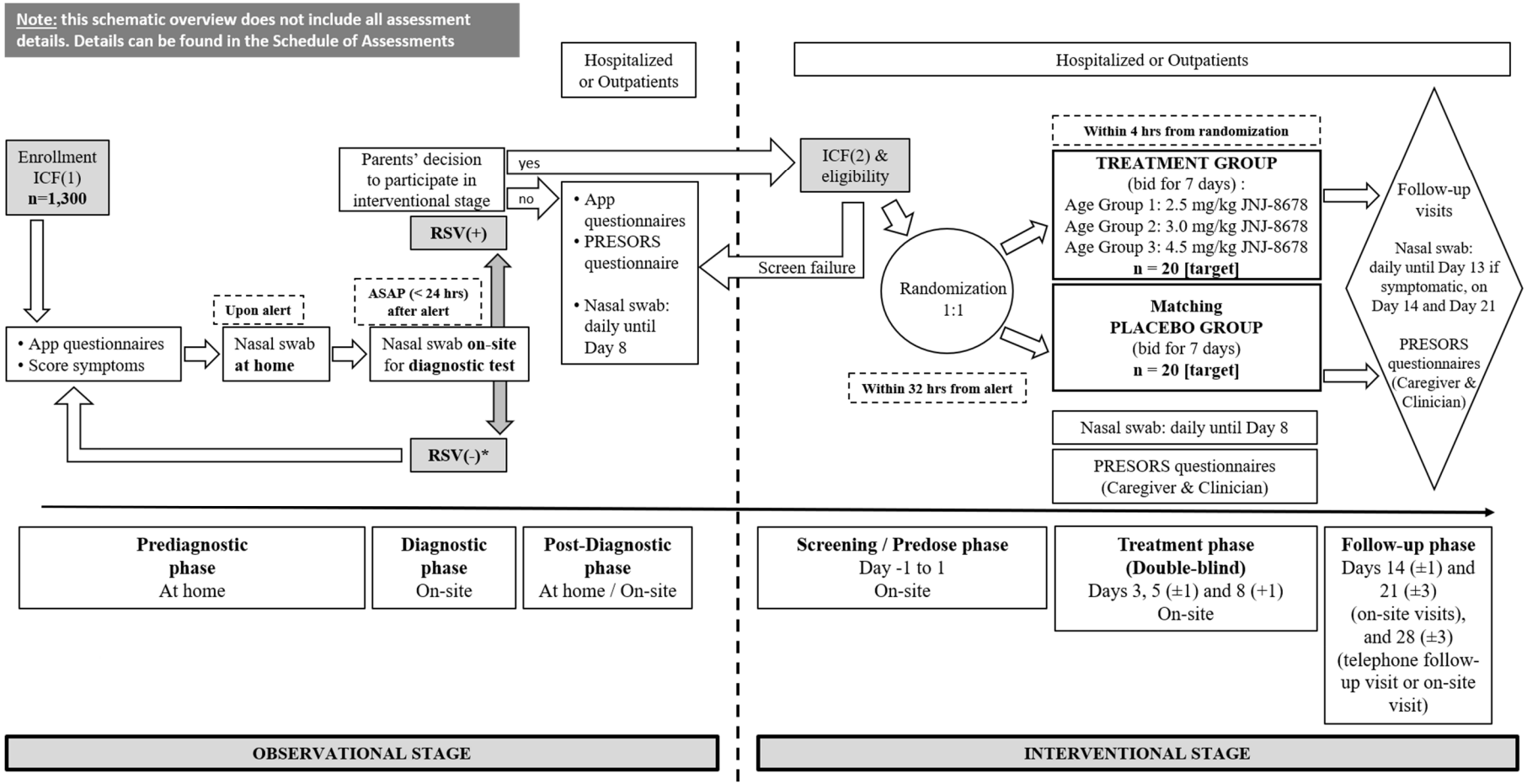
Interim analyses may be performed at the sponsor's discretion to support decision making for further development of JNJ-53718678 and to support interactions with health authorities.

In case of an interim analysis, investigators, participants' parents/caregivers, and local sponsor representatives will remain blinded. The sponsor leadership team responsible for decisions and the central study team required to generate and interpret results will have access to unblinded data.

1.2. Schema

Figure 1: Schematic Overview of the Design of the Study

Note: Prior to Protocol Amendment 2, the total daily dose was the same but the daily dosing frequency was qd instead of bid.



*If the participant is RSV(-) at the RSV-like acute respiratory infection (ARI) visit, the parent(s)/caregiver(s) will continue completion of the mobile App questions, alerts will be paused for 7 days.

bid=twice daily; ICF=informed consent form; PRESORS= Pediatric RSV Electronic Severity and Outcome Rating System; RSV= respiratory syncytial virus

1.3. Schedule of Activities (SoA)

Part 1: Observational Stage – Enrollment to Diagnosis

Phase	**Pre-diagnosis**		**Diagnosis**	
Period	**Enrollment**	**RSV mobile App alert[a]**	**RSV-like ARI Visit[b,c]**	
Timeframe			**Observational Stage Day 1 (RSV diagnostic test to be performed at site as soon as possible but no later than 24 hours after receipt of RSV mobile App alert)**	**RSV alert day +21 days (+2wks)**
Study Procedures				
Informed consent (ICF)[d]	X			
ICF for optional blood sampling[e,f]			X	
ICF for optional buccal swab collection (for genetic analyses)[e]	X			
ICF for optional stool sampling[e]	X			
Demographics	X			
Review medical history	X			
Inclusion/exclusion criteria	X			
Training parent(s)/caregiver(s) for nasal sampling at home[g]	X			
RSV diagnostic test			X	
Systolic and diastolic blood pressure[h]			X	
Complete physical examination[i]			X	
Clinical evaluation[j]			X	
Use of RSV mobile App by parent(s)/caregiver(s)[k]	Continuous [l]			
Monitoring of RSV mobile App dashboard by site staff, and take action where needed[m]	Continuous [l]			
Completion of questionnaires by parent(s)/caregiver(s)	Continuous [l]			
Buccal swab collection (optional)	X[n]			
Blood sample collection (optional)			X[o]	
Stool sample collection (optional)	X[p]			X[q]
Mid-turbinate nasal swab[r] • at home • at the site		X	X[s]	

Phase	Pre-diagnosis		Diagnosis	
Period	**Enrollment**	**RSV mobile App alert[a]**	**RSV-like ARI Visit[b,c]**	
Timeframe			**Observational Stage Day 1 (RSV diagnostic test to be performed at site as soon as possible but no later than 24 hours after receipt of RSV mobile App alert)**	**RSV alert day +21 days (+2wks)**
Study Procedures				
Concomitant medication	X		X	
Adverse events[t]	Continuous			

Footnotes:

a Once the RSV mobile Application (App) is activated, pre-programmed study-related questions (App questionnaires) will be asked via the parent/caregiver's smartphone twice daily (bid). The answers of the parent(s)/caregiver(s) will drive an algorithm that calculates scores in the background of the application, where the threshold score is defined on the basis of the presence of the signs and symptoms per eligibility criteria for intervention, thus a combination of an upper and a lower respiratory sign and a sign of systemic impact. When the infant starts showing clinical signs compatible with RSV disease, that cross this threshold score in the RSV mobile App the parent(s)/caregiver(s) will receive an alert asking them to collect a nasal swab at home and to invite them to present to the site with their infant for a study visit as soon as possible, ie, within <24 hours after the receipt of the alert (RSV-like acute respiratory infection [ARI] visit). A mid-turbinate nasal swab will be collected at the site by qualified study-site personnel and tested with a study-related RSV molecular-based diagnostic assay to diagnose RSV.

b The ARI visit (Observational Stage Day 1) should take place at the study site.

c RSV negative participants (RSV[-]) will re-enter and continue in the pre-diagnostic phase and the parent(s)/caregiver(s) will observe the health condition of the infant and answer the App questionnaires on the RSV mobile App until the next alert or until the end of the RSV circulation as defined per country/region/site.

d The ICF for the observational stage of the study must be signed at enrollment and no later than before the first study-related activity is performed.

e Refusal to give consent for the optional samples does not exclude a participant from participation in the study.

f The ICF should preferably be signed at Day 1 but can be signed at any time after consent to participate in the study is given, but before blood sampling is performed.

g If re-training is needed, this will be performed at a later time point.

h Systolic and diastolic blood pressure need to be measured supine (preferably the same position at each measurement) after at least 5 minutes of rest.

i Physical examination of all body systems, including length and head circumference and body weight measurement and skin examination.

j Clinical evaluation includes measurements/evaluations of respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2), need for and duration of hospitalization, occurrence of complications, need for antibiotics. In case of hospitalization, the following additional evaluations will be performed: oxygen requirement (type and duration), level of and duration of hospital care, hydration/feeding by intravenous (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).

k The RSV mobile App will be downloaded on the parent/caregiver's own smartphone during the enrollment visit or at any time after signing the ICF. The RSV mobile App will be used from a predefined date (start date will be country and site dependent) until study completion.

l Participants for whom the threshold for an alert for an ARI visit is never reached and participants who are diagnosed RSV(-) after an alert will be followed until the end of the RSV circulation.

m The dashboard will need monitoring by the site staff during the entire period of the study from the activation of the questions in the RSV mobile App until completion of the observational part of the study. In case of alerts or incompliances notified in the dashboard, it is the site's responsibility to follow-up with the parent(s)/caregiver(s) of the specific participant to discuss compliance to protocol requirements, such as taking nasal sampling, planning site visit, completion of questionnaires.

n An optional buccal swab will be taken from all participants whose parent(s)/caregiver(s) have provided additional consent.

o An optional blood sample for exploratory biomarker analyses will be collected from all participants that have an RSV-like ARI visit (collection only at the first RSV-like ARI visit if multiple), irrespective of RSV(+) or RSV(-) diagnosis, if consent for blood sampling is provided. The blood sample should be obtained by phlebotomy/venipuncture.

p Optional stool samples will be taken from all participants whose parent(s)/caregiver(s) have provided additional consent. Stool samples from the infant will be collected by the parent(s)/caregiver(s) in dedicated sampling tubes at enrollment (+2 weeks; healthy baseline) and at the age of 4 months (±2 weeks; unless this age coincides with enrollment, ie, within 2-week window; in that case only 1 sample is to be collected) for participants in the observational stage. Information on date and time of stool sampling as well as feeding type (liquid vs solid) and composition (eg, milk, vegetables, fruit, meat/fish) will be collected. When participants are hospitalized, the collection of samples and information on date and time as well as feeding type and composition will be collected by the site staff.

q An optional stool sample will be collected for participants with an ARI alert, who did not enter the interventional stage of the study, at 21 days (+2 weeks) after the ARI alert unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected. For RSV(-) participants, in case another ARI alert is triggered within 2 weeks after the first alert only 1 stool sample needs to be collected. If this second alert results in a positive RSV diagnosis, the stool sample should preferably be collected at 21 days (+2 weeks) after the RSV(+) diagnosis.

r During the enrollment visit of the infant, the infant's nostrils will be assessed for septum deviations or malformations by the investigator or his/her designee before the first nasal sampling. Mid-turbinate nasal swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding).

s If the diagnostic nasal mid-turbinate sample during the RSV-like ARI visit is taken within 4 hours from the sample for testing at home, the nasal mid-turbinate swab sample during the RSV-like ARI visit should be taken from the other nostril. In that case nasal mid-turbinate swab samples should be continued to be collected from the same nostril as used during the RSV-like ARI visit.

t All serious and non-serious adverse events related to the study sampling procedures and all deaths (including their causality) will be documented and will be communicated according to the procedure that will be provided by the sponsor.

Part 1: Observational Stage – RSV(+) Outpatients[a] NOT Enrolled in Interventional Stage (Including Screen Failures of the Interventional Stage)

Phase	Day of Diagnosis	Post-diagnosis			
Observational Stage Day	**1**	**2-8**	**9-14**	**15-20**	**21 End-of-study (±3 days)[h]**
Study Procedures					
Administrative					
ICF for optional blood sampling[b]	(X)[c]				
Viral Load Kinetics					
Mid-turbinate nasal swab[d,e]		X			
Clinical Assessments					
Clinical evaluation[f]	(X)[c]				
Clinician PRESORS	X				
Parent(s)/caregiver(s) PRESORS	X	bid	bid	X	X
Use of RSV mobile App by parent(s)/caregiver(s)	Continuous				
Completion of App questionnaires by parent(s)/caregiver(s)	Continuous				
Monitoring of RSV mobile App dashboard and of parent(s)/caregiver(s) PRESORS completion by site staff	Continuous				
Clinical Laboratory Assessments					
Blood sample collection (optional)	(X)[c]				
Stool sample collection (optional)[g]					X
Ongoing Participant Review					
Adverse events	Continuous				
Concomitant medication	Continuous				

Footnotes:

a. For outpatients who 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 Schedule of Activities for RSV(+) hospitalized patients NOT enrolled in interventional stage, if practically feasible.

b. The ICF must be signed before (optional) blood sampling is performed.

c. The assessments on the day of diagnosis (Day 1) will only be performed once.

d. Mid-turbinate nasal swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Nasal swabs will be collected daily through Observational Stage Day 8 for RSV viral load determination. The time and date of the nasal swab collection will be recorded. The investigator/study site personnel will train the parent(s)/caregiver(s) to collect the mid-turbinate nasal swab. Detailed information on sample collection is available in Section 8.3.1.

e. Leftover mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at discretion of the sponsor.

f. 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. All clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding).
g. Stool samples from the infant will be optionally collected by the parent(s)/caregiver(s) at 21 days (+2 weeks) after the ARI alert unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected. Information on date and time of stool sampling as well as feeding type (liquid vs solid) and composition (eg, milk, vegetables, fruit, meat/fish) will be collected.
h. End of study will be 21 days (+2 weeks) in case optional stool samples will be collected (the additional time is only for optional stool sample assessments).

Part 1: Observational Stage – RSV(+) Hospitalized Patients[a] NOT Enrolled in Interventional Stage up to Discharge (Including Screen Failures of the Interventional Stage)

Phase	Day of Diagnosis	Post-diagnosis			
Observational Stage Day	**1**	**2-8**	**9-14**	**15-20**	**21 End-of-study (±3 days)[h]**
Study Procedures					
Administrative					
ICF for optional blood sampling[b]	(X)[c]				
Viral Load Kinetics					
Mid-turbinate nasal swab[d,e]		X			
Clinical Assessments					
Clinical evaluation[f]	(X)[c]	bid	bid	bid	bid
Clinician PRESORS	X	bid	bid	X	X
Parent(s)/caregiver(s) PRESORS	X	bid	bid	X	X
Use of RSV mobile App by parent(s)/caregiver(s)	Continuous				
Completion of App questionnaires by parent(s)/caregiver(s)	Continuous				
Monitoring of RSV mobile App dashboard and of parent(s)/caregiver(s) PRESORS completion by site staff	Continuous				
Clinical Laboratory Assessments					
Blood sample collection (optional)	(X)[c]				
Stool sample collection (optional)[g]					X
Ongoing Participant Review					
Adverse events	Continuous				
Concomitant medication	Continuous				

Footnotes:

a For participants who are discharged during the course of the study, consecutive assessments should be performed according to the Schedule of Activities for RSV(+) outpatients NOT enrolled in interventional stage.

b The ICF must be signed before blood sampling is performed.

c The assessments on the day of diagnosis (Day 1) will only be performed once.

d Mid-turbinate nasal swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Nasal swabs will be collected daily through Observational Stage Day 8 for RSV viral load determination. The time and date of the nasal swab collection will be recorded. For RSV(+) patients who are hospitalized after Observational Stage Day 8, an additional nasal swab will be collected at day of discharge. Detailed information on sample collection is available in Section 8.3.1.

e Leftover mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at discretion of the sponsor.

f 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).

g Stool samples from the infant will be optionally collected by the site staff at 21 days (+2 weeks) after the ARI alert unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected. Information on date and time of stool sampling as well as feeding type (liquid vs solid) and composition (eg, milk, vegetables, fruit, meat/fish) will be collected by the site staff.

h End of study will be 21 days (+2 weeks) in case optional stool samples will be collected (the additional time is only for optional stool sample assessments).

Part 2: Interventional Stage – Outpatients[a]

Phase	Screening Phase	Treatment Phase							Follow-up[b]					
Day[c]	-1 to 1[d]	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
	On-site visit	Treatment On-site		On-site visit[e]		On-site visit[e]		On-site visit[e]		On-site visit[e]		On-site visit[e]		Phone follow-up/ Conditional[f] on-site visit
Study Procedures														
Administrative														
ICF for interventional stage of the study	X													
Eligibility criteria	X[g]													
Participant characteristics and demographics	X													
Medical history/prior medications	X													
Randomization		X[h]												
Study Medication Administration														
Dosing study medication[i]		bid	bid	bid	bid	bid	bid							
Provision of study medication for daily use at home[j]		X												
Document dosing[k]		bid	bid	bid	bid	bid	bid							
Efficacy Assessments														
Clinical evaluation[l]		X		X		X		X		X		X		(X)[m]
Clinician PRESORS	X	X		X		X		X		X		X		
Parent(s)/caregiver(s) PRESORS[n]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid	X	X[o]		
Temperature log completion[p]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid	X	X		

Phase	Screening Phase	Treatment Phase							Follow-up[b]					
Day[c]	-1 to 1[d]	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
	On-site visit	Treatment On-site		On-site visit[e]		On-site visit[e]		On-site visit[e]		On-site visit[e]		On-site visit[e]		Phone follow-up/ Conditional[f] on-site visit
Monitoring of parent(s)/caregiver(s) PRESORS completion by site staff	Continuous													
Mid-turbinate nasal swab[q,r,s]	X[t]		X	X	X	X	X	X	X	X		X		
Nasal swab log completion			X		X		X		X					
Safety Assessments														
Systolic and diastolic blood pressure[u]	X			X		X		X		X		X		(X)[m]
Directed physical examination[v]				X				X		X		X		(X)[m]
ECG (triplicate 12-lead)[w]	X	X[x]		X[x]				X				X[x]		(X)[m,x]
Clinical Laboratory Assessments														
Blood sampling for hematology and biochemistry[y]	X[y]							X[y]		X[z]				(X)[m,aa]
Urinalysis[bb]	X							X		X[z]				(X)[m,aa]
Pharmacokinetics														
Blood sampling for PK of JNJ-53718678[cc]		X		(X)		(X)								
Ongoing Participant Review														
Adverse events	Continuous													
Concomitant medication	Continuous													(X)[m]

Footnotes:

a For outpatients who 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 Schedule of Activities for hospitalized patients, if practically feasible.

b In case participants prematurely discontinue study medication treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the participant's remaining study visits and assessment schedule or, at a minimum, to return with the participant 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 participant'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 Visit windows should be applied only for logistical reasons. There should be at least 1 day between 2 consecutive planned site visits.

d Screening/predose assessments can only start after signing of the ICF for the interventional stage and before randomization. All screening/predose procedures should take place prior to the first study medication intake. For analysis purposes, the day of first study medication intake will be considered Day 1 of the interventional stage.

e 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).

f In case a participant is experiencing (an) ongoing adverse event(s) or has clinically significant laboratory 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 participant at the site (preferred option) or, if feasible for the study site and if allowed per local regulations, at home on Day 28 (±3).

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

h Randomization should occur within 32 hours after the receipt of the RSV mobile App alert. Randomization is to occur predose.

i Study medication administration should start as soon as possible, but within 4 hours after randomization. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For participants 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 participants 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 medication can be administered with/without food. The study medication will be administered orally using a dosing syringe.

j Study site personnel will train participants' parent(s)/caregiver(s) on how to use and store the study medication for at home dosing. Study medication will be provided at Day 1 in 1 single vial, from which the assigned volume is to be withdrawn each day, for the remainder of the study.

k Date and time of study medication dosing and volume administered will be recorded in the eCRF or in the study medication log.

l 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. All clinical assessments should preferably be done when the infant is calm (ie, not crying or immediately after feeding).

m Only applicable in case of on-site visit.

n The first parent(s)/caregiver(s) PRESORS assessment of the bid schedule on Day 1 needs to be completed as close as feasibly possible and prior to the first administration of study medication. Detailed information is available in Section 8.3.3.

o The parent(s)/caregiver(s) PRESORS have to be completed by the participant's parent(s)/caregiver(s) during Day 21 visit as the first activity of the visit prior to any other procedures.

p Body temperature to be measured and recorded by parent(s)/caregiver(s). In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.

q One mid-turbinate nasal swab will be taken of which aliquots will be used for a central laboratory confirmation of RSV infection (Day 1 predose only), 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 co-pathogens (Day 1 predose only).

r Mid-turbinate nasal swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Nasal swabs will be collected daily

through Day 8 in all participants. The investigator/study site personnel will train the parent(s)/caregiver(s) to collect the mid-turbinate nasal swab in case collection by a healthcare professional (HCP) is not possible. As of Day 8, in participants who were symptomatic based on the clinician PRESORS at Day 8, daily swabs will be collected through Day 13 or until the participant 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 mid-turbinate nasal swab will be collected during the scheduled visit for all participants. Detailed information on sample collection is available in Section 8.3.2.

s Leftover mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at discretion of the sponsor.

t The mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study medication (on Day 1). If the RSV-like ARI visit nasal swab taken at the site was taken less than 8 hours prior to start of dosing, then this sample can be used as the Day 1 predose sample, and no additional nasal sample needs to be collected at Day 1 predose.

u Systolic and diastolic blood pressure need to be measured supine (preferably the same position at each measurement) after at least 5 minutes of rest.

v Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.

w Triplicate 12-lead electrocardiograms (ECGs) will be obtained for central reading. 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 time point as other assessments, the ECG should be performed first.

x At Day 1 and Day 3, triplicate ECGs should be obtained approximately one hour after administration of study drug. At Day 28, triplicate 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 to confirm abnormal ECG findings, unscheduled ECGs should be obtained.

y Samples for clinical laboratory assessments, including for levels of potassium and magnesium, will be collected and analyzed at the local laboratory at the site. 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 and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values) may be required.

z Assessments will only be performed in case of any clinically significant laboratory abnormalities observed at Day 8.

aa Only to be performed in case any adverse event observed on Day 21 requires additional clinical laboratory assessments.

bb Urinalysis will be performed by the local laboratory.

cc A blood sample for determination of JNJ-53718678 concentrations will be collected by the site staff through finger prick or heel stick on Day 1 and Day 3 or Day 5. On Day 1, the PK samples should be collected approximately one hour after first administration of study drug (after the ECGs are obtained). On Day 3 or Day 5, the PK samples should be collected at least 4 hours after the AM and prior to the PM dosing on that day. Date and time of study medication intake, date and time of PK blood sampling, and time of meal if any in the time window of 30 minutes before and 30 minutes after study medication intake on the day of PK sampling need to be recorded.

Note 1: Additional unscheduled visits in case of lab abnormalities, ECG abnormalities, need for clinical follow-up of (an) adverse event(s) can be scheduled at the discretion of the investigator.

Note 2: Refer to Section 10.7, Appendix 7 for guidance on study conduct during the COVID-19 pandemic.

Part 2: Interventional Stage - Hospitalized Patients up to Discharge[a]

Phase	Screening Phase	Treatment Phase					Follow-up[b]					
Day	-1 to 1[c]	1	2[d]	3	4-7	8 (+1)	9-13	14 (±1)	15-20	21 (±3)	22-27	28 (±3) End-of-study
												Phone follow-up/ Conditional[e] on-site visit
Study Procedures												
Administrative												
ICF for interventional stage of the study	X											
Eligibility criteria	X[f]											
Participant characteristics and demographics	X											
Medical history/prior medications	X											
Randomization		X[g]										
Study Medication Administration												
Dosing study medication and document dosing[h]		bid	bid	bid	bid							
Provision of study medication or daily use at home at discharge, if applicable[i]			(X)	(X)	(X)							
Efficacy Assessments												
Clinical evaluation[j]		bid	bid	bid	bid	bid	bid	bid	bid	bid		(X)[k]
Clinician PRESORS	X	bid	bid	bid	bid	bid	bid	bid	X	X		
Parent(s)/caregiver(s) PRESORS[l]	X	bid	bid	bid	bid	bid	bid	bid	X	X[m]		
Monitoring of parent(s)/caregiver(s) PRESORS completion by site staff	Continuous											
Mid-turbinate nasal swab[n,o,p]	X[q]		X	X	X	X	X	X		X		
Safety Assessments												
Systolic and diastolic blood pressure[r]	X	bid	bid	bid	bid	bid	bid	bid	bid	bid		(X)[k]
Directed physical examination[s]				X		X		X		X		(X)[k]
ECG (triplicate 12-lead)[t]	X	X[u]		X[u]		X				X[u]		(X)[k,u]
Clinical Laboratory Assessments												
Blood sampling for hematology and biochemistry[v]	X[v]					X[v]		X[w]				(X)[k,x]
Urinalysis[y]	X					X		X[w]				(X)[k,x]

Phase	Screening Phase	Treatment Phase					Follow-up[b]					
Day	**-1 to 1[c]**	**1**	**2[d]**	**3**	**4-7**	**8 (+1)**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**22-27**	**28 (±3) End-of-study**
												Phone follow-up/ Conditional[e] on-site visit
Pharmacokinetics												
Blood sampling for PK of JNJ-53718678[z]		X		(X)	(X)							
Ongoing Participant Review												
Adverse events	Continuous											
Concomitant medication	Continuous											(X)[k]

Footnotes:

a For participants who are discharged during the course of the study (as of Day 2), consecutive assessments should be performed according to the Schedule of Activities for hospitalized patients after discharge.

b In case participants prematurely discontinue study medication treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the participant's remaining study visits and assessment schedule, or, at a minimum, to return with the participant 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 participant'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 for the interventional stage and before randomization. All screening/predose procedures should take place prior to the first study medication 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 medication intake will be on that day, immediately after establishing eligibility. For analysis purposes, the day of first study medication intake will be considered Day 1 of the interventional stage.

d Participants 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 Participant's parent(s)/caregiver(s) will be contacted by site staff for a telephone follow up visit. In case a participant is experiencing (an) ongoing adverse event(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.

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

g Randomization should occur within 32 hours after the receipt of the RSV mobile App alert. Randomization is to occur predose.

h Study medication administration should start as soon as possible, but within 4 hours after randomization. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For participants 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 participants 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 medication can be administered with/without food. The study medication will be administered orally using a dosing syringe. Date and time of study medication dosing and volume administered will be recorded in the eCRF.

i Study site personnel will instruct participants' parent(s)/caregiver(s) on how to use and store the study medication for at-home dosing on the day of discharge, if applicable. Study medication 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 study.

j 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).

k Only applicable in case of on-site visit.

l The first parent(s)/caregiver(s) PRESORS assessment of the bid schedule on Day 1 needs to be completed as close as feasible and prior to the first administration of study medication. Detailed information is available in Section 8.3.3.

m The parent(s)/caregiver(s) PRESORS have to be completed by the participant's parent(s)/caregiver(s) during Day 21 visit as the first activity of the visit prior to any other procedures.

n One mid-turbinate nasal swab will be taken of which aliquots will be used for a central laboratory confirmation of RSV infection (Day 1 predose only), 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 co-pathogens (Day 1 predose only).

o Mid-turbinate nasal swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). Nasal 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 8.3.2.

p Leftover mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at discretion of the sponsor.

q The mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study medication (on Day 1). If the RSV-like ARI visit nasal swab taken at the site was taken less than 8 hours prior to start of dosing, then this sample can be used as the Day 1 predose sample, and no additional nasal sample needs to be collected at Day 1 predose.

r Systolic and diastolic blood pressure need to be measured supine (preferably the same position at each measurement) after at least 5 minutes of rest.

s Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.

t Triplicate 12-lead ECGs will be obtained for central reading. 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 time point as other assessments, the ECG should be performed first.

u At Day 1 and Day 3, triplicate ECGs should be obtained approximately one hour after administration of study drug. At Day 28, triplicate 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 to confirm abnormal ECG findings, unscheduled ECGs should be obtained.

v Samples for clinical laboratory assessments, including for levels of potassium and magnesium, will be collected and analyzed at the local laboratory at the site. 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 and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values) may be required.

w Assessments will only be performed in case of any clinically significant laboratory abnormalities observed at Day 8.

x Only to be performed in case any adverse event observed on Day 21 requires additional clinical laboratory assessments.

y Urinalysis will be performed by the local laboratory.

z A blood sample for determination of JNJ-53718678 concentrations will be collected by the site staff through finger prick or heel stick on Day 1 and on Day 3 or Day 5. On Day 1, the PK samples should be collected approximately one hour after first administration of study drug (after the ECGs are obtained). On Day 3 or

Day 5, the PK samples should be collected at least 4 hours after the AM and prior to the PM dosing on that day. Date and time of study medication intake, date and time of PK blood sampling, and time of meal if any in the time window of 30 minutes before and 30 minutes after study medication intake on the day of PK sampling need to be recorded.

Note 1: Additional unscheduled visits in case of lab abnormalities, ECG abnormalities, need for clinical follow-up of (an) adverse event(s) can be scheduled at the discretion of the investigator.

Note 2: Refer to Section 10.7, Appendix 7 for guidance on study conduct during the COVID-19 pandemic.

Part 2: Interventional Stage - Hospitalized Patients 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 Medication Administration												
Dosing study medication and document dosing[e]		bid	bid	bid	bid							
Efficacy Assessments												
Clinical evaluation[f]		X		X		X		X		X		(X)[g]
Clinician PRESORS		X		X		X		X		X		
Parent(s)/caregiver(s) PRESORS	bid[h]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	X	X[j]		
Temperature log completion[k]	bid[h]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	bid[i]	X	X		
Monitoring of parent(s)/caregiver(s) PRESORS completion by site staff	Continuous											
Mid-turbinate nasal swab[l,m]		X	X	X	X	X	X	X		X		
Nasal swab log completion			X		X		X					
Safety Assessments												
Systolic and diastolic blood pressure[n]		X		X		X		X		X		(X)[g]
Directed physical examination[o]		X				X		X		X		(X)[g]
ECG (triplicate 12-lead)[p]		X[q]				X				X[q]		(X)[g,q]
Clinical Laboratory Assessments												
Blood sampling for hematology and biochemistry[r]						X[r]		X[s]				(X)[g,t]
Urinalysis[u]						X		X[s]				(X)[g,t]
Pharmacokinetics												
Blood sampling for PK of JNJ-53718678[v]		(X)		(X)								
Ongoing Participant Review												
Adverse events	(X)	Continuous										
Concomitant medication	(X)	Continuous										(X)[g]

Footnotes:

a When participants 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 Schedule of Activities for hospitalized patients, if practically feasible.

b In case participants prematurely discontinue study medication treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the participant's remaining study visits and assessment schedule, or, at a minimum, to return with the participant 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 participant'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 Participant's parent(s)/caregiver(s) will be contacted by site staff for a telephone follow up visit. In case a participant is experiencing (an) ongoing adverse event(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 participant 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 Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For participants 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 participants receive 14 consecutive doses in total. The study medication can be administered with/without food. The study medication will be administered orally using a dosing syringe. Date and time of study medication dosing and volume administered will be recorded in the eCRF or in the study medication log.

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 Only applicable in case of on-site visit.

h The morning assessment needs to be done prior to discharge and the evening one should be done at home.

i If the participant is discharged prior to completion of the last assessment of the bid schedule, this last assessment should be performed at home.

j The parent(s)/caregiver(s) PRESORS have to be completed by the participant's parent(s)/caregiver(s) during Day 21 visit as the first activity of the visit prior to any other procedures.

k Body temperature to be measured and recorded by parent(s)/caregiver(s). In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.

l Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). After discharge, nasal swabs will be collected daily through Day 8 in all participants. As of Day 8, in participants who were symptomatic based on the clinician PRESORS at Day 8, daily nasal swabs will be collected through Day 13 or until the participant 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 mid-turbinate nasal swab will be collected during the scheduled visit for all participants. Detailed information on sample collection is available in Section 8.3.2.

m Leftover mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at discretion of the sponsor.

n Systolic and diastolic blood pressure need to be measured supine (preferably the same position at each measurement) after at least 5 minutes of rest.

o Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.

p Triplicate 12-lead ECGs will be obtained for central reading. 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.

q At Day 3, triplicate ECGs should be obtained approximately one hour after administration of AM study drug. At Day 28, triplicate 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 to confirm abnormal ECG findings, unscheduled ECGs should be obtained.

r Samples for clinical laboratory assessments, including for levels of potassium and magnesium, will be collected and analyzed at the local laboratory at the site. In case of hypokalemia or hypomagnesemia at Day 8, the levels of potassium and magnesium should be checked as soon as possible and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values) may be required.

s Assessments will only be performed in case of any clinically significant laboratory abnormalities observed at Day 8.

t Only to be performed in case any adverse event observed on Day 21 requires additional clinical laboratory assessments.

u Urinalysis will be performed by the local laboratory.

v A blood sample for determination of JNJ-53718678 concentrations will be collected by the site staff through finger prick or heel stick on Day 3 or Day 5. The PK samples should be collected at least 4 hours after the AM and prior to the PM dosing on that day. Date and time of study medication intake, date and time of PK blood sampling, and time of meal if any in the time window of 30 minutes before and 30 minutes after study medication intake on the day of PK sampling need to be recorded.

Note 1: Additional unscheduled visits in case of lab abnormalities, ECG abnormalities, need for clinical follow-up of (an) adverse event(s) can be scheduled at the discretion of the investigator.

Note 2: Refer to Section 10.7, Appendix 7 for guidance on study conduct during the COVID-19 pandemic.

2. 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.[5] 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.[1,26]

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.[27] RSV infection can cause considerable morbidity and mortality in certain patient populations such as infants[19] where RSV can lead to 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.[17,18]

RSV is a major cause of hospital admissions and death in young children worldwide.[19,23] 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.[6] 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.[24]

On the other hand, among children <5 years of age with RSV infection, 97.7% present for medical care as outpatients in emergency departments (EDs) and in pediatric practices, while 2.7% require hospitalization.[9] 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.[15] These rates of visits for RSV-associated acute respiratory infections (ARIs) suggest that a major proportion of the burden of RSV results in outpatient visits among children beyond infancy.[9]

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.[1,22] 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.[4,25] 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.

RSV-related acute respiratory tract infection in children is often a self-resolving disease that mostly occurs at home, imposing a high burden on family and society. Although virtually all children will have been infected with RSV at least once by the age of 2 years,[8] there is still limited parental awareness about RSV disease.

The duration and level of distress and anxiety of the parent/caregiver due to severe RSV infection are underestimated.[16] Bronchiolitis symptoms usually peak around Day 3 to Day 5 and in case of early presentation (Day 2) at the general practitioner or ED, it can be expected that the child may get worse before getting better. Furthermore, about half of the children who develop severe disease do so after their first ED visit, often in the absence of clear instructions for parents when discharged home.[3] Current guidelines recommend that the parents monitor the child at home pre- and post-discharge, with focus on severe to very severe symptoms, while most children present moderate to severe disease resulting in high discomfort for child and family.[20,21] Therefore, there is a need to improve RSV disease symptom awareness and appropriate mobilization of parent/caregivers to present their infant for medical care at the onset of disease, to allow the optimal timing of new antiviral therapeutic interventions based on primary antiviral activity.

2.1. Study Rationale

RSV is considered the most important virus causing acute LRTI and a major cause of hospital admissions and death in young children worldwide.[19,23] Infants born prematurely or close to the RSV circulation and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI. At the time of RSV intercept when the infants are brought in (on the parent/caregiver's initiative) for medical care for an ARI, the RSV viral load is mostly already past its peak and declining[7], whereas the disease can still evolve. In order to have a significant effect on the disease severity, treatment needs to be started as soon as possible to prevent further replication of the virus and the ensuing inflammatory response leading to the clinical signs/symptoms and to maximize the potential for the study medication to exert its antiviral effects, thereby affecting the clinical course of the disease.

This study is designed to assess in the setting of a planned early interception of pediatric RSV disease, early viral and disease kinetics (observational stage) and the antiviral effects of an RSV fusion inhibitor, JNJ-53718678 (interventional stage). In the observational stage the infant is closely monitored for early symptoms by the parent(s)/caregiver(s) and thus may be brought in for diagnosis earlier than in the typical setting.

2.2. Background

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.[2,17] 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 medication 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 participants hospitalized due to RSV-infection (Study 53718678RSV1005).

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 medication 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 I_{Kr} was present at 10 μM M5,

but not at 1 and 3 µM. When JNJ-53718678 was administered intravenously (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 were increased at all doses in most dogs and blood pressure 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 [$AUC_{0\text{-}7h}$]=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 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 body weight 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, AST and decreased albumin. Red blood cell (RBC) parameters and platelets were decreased while reticulocytes were increased. Changes in white blood cell (WBC) 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, body weight loss in relation with decreased 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 body weight 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 WBCs and RBCs, leading to hemosiderin deposition in the liver and adaptive changes in hematopoietic organs (bone marrow [BM], spleen). The effects on WBCs and RBCs 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 body weight 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 body weight 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 body weight 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 body weight 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 body weight 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 $AUC_{0\text{-}24h}$ 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 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 participants.

In Study 53718678RSV1009, the effect of JNJ-53718678 on the cardiac repolarization interval in healthy adult participants 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 placebo-corrected change from baseline for the 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.[14] A change to a twice daily (bid) dosing regimen (see Section 4.3) and several other mitigation measures to safeguard the participants (see Section 2.3.5) have been implemented.

Multiple Dose

Adult Population

In the multiple-dose escalation part of Study 53718678RSV1001 in adult participants 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 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 participants, the pharmacokinetic (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 participants 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}, minimum plasma concentration (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 hour to 3.5 hours 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 the ongoing 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 participants 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 participants 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 participants 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 participants receiving the oral solution, no deaths or other serious adverse events (AEs) were reported; 4 participants discontinued study treatment due to an AE. Among participants who received at least 1 dose of JNJ-53718678, 70% experienced an AE as compared to 46.7% of all participants 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 participant who received placebo was reported with a Grade 3 headache in Study 53718678RSV1001. AEs observed more frequently (difference in incidence of ≥5%) in participants who had received at least 1 dose of JNJ-53718678 compared to participants 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 participants receiving JNJ-53718678 and in none of the participants 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 multiple

dose escalation (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 participants who had received at least 1 dose of JNJ-53718678 compared to participants 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 participants 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 participants and were considered generally clinically insignificant. These were either Grade 1 or Grade 2 in severity, except for 1 participant 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 participants receiving JNJ-53718678 compared to participants receiving placebo.

No prolongations of the QT interval corrected for heart rate according to Fridericia's formula (QTcF) were reported. Changes in 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 participants inoculated with RSV, JNJ-53718678 at single doses up to 1,000 mg JNJ-53718678 and multiple doses up to 500 mg JNJ-53718678 qd and 250 mg JNJ-53718678 bid, 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 participants (n=12) from the study part evaluating the oral suspension in the ongoing Study 53718678RSV1007, 10 participants (76.9%) were reported with at least 1 AE. The incidence of AEs was similar between the different treatments: 5 (41.7%) participants receiving the oral solution and 6 (50%) and 4 (30.8%) participants 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 participants) were diarrhea (3 participants [25.0%] receiving the JNJ-53718678 oral solution, 1 participant [8.3%] receiving the suspension under fasted conditions, and 1 participant [7.7%] receiving the suspension under fed conditions) and oropharyngeal pain (1 participant [8.3%] receiving the

JNJ-53718678 oral solution and 2 participants [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 participant who received the JNJ-53718678 suspension under fasted conditions and 1 other participant 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 medication.

Abnormalities in vital signs and ECG-parameters were observed in few participants (2 participants 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 participants. 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 participants. No clinically significant safety findings were identified in any participants 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 participants 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 participants who received placebo. Diarrhea, nausea, and headache were more frequently observed in participants who received JNJ-53718678 compared to participants who received placebo.

Safety results from Part 2 (TQT part) of Study 53718678RSV1009 demonstrated that JNJ-53718678 was generally safe and well tolerated in healthy adult participants. 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 participants:

- One participant 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 participant 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 participant 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%) participants after receiving 500 mg JNJ-53718678, 22 (88.0%) participants after receiving 4,500 mg JNJ-53718678, 9 (39.1%) participants after receiving placebo, and 12 (50.0%) participants after receiving 400 mg moxifloxacin. During the treatment phase, diarrhea, nausea, and headache were more frequently observed in participants who received 4,500 mg of JNJ-53718678 compared to participants 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.[14] A change to a bid dosing regimen (see Section 4.3) and several other mitigation measures to safeguard the participants (see Section 2.3.5) 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 participant, 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 participants (4,500 mg JNJ-53718678 and placebo) had an abnormal QTcF value between 450 and 480 ms, leading to early study discontinuation for 1 participant due to AE.
- Six participants 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 participants 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 the study. Overall, 55.6% of participants 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 participants (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 participants.

Pediatric Population

In Study 53718678RSV1005 in pediatric participants receiving the oral solution, no deaths, Grade 4 AEs, or AEs leading to study discontinuation or permanent stop of study medication were reported. Four SAEs 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 medication. The majority of participants were reported with at least 1 AE, at similar incidence rates in both treatment arms (28/37 participants [75.7%] in the JNJ-53718678 [combined] treatment group vs 6/7 participants [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 participants receiving JNJ-53718678 (reported in ≥10% of participants) were vomiting, upper respiratory tract infection, and feces soft. AEs reported in ≥10% (ie, ≥4 participants) of participants receiving JNJ-53718678 that were considered by the investigator to be at least possibly related to study medication 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 medication 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 participant (placebo) was reported with the Grade 1 AE of tachycardia considered not related to study medication by the investigator. ECG abnormalities were scarce and generally not considered clinically relevant. One participant (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 medication by the investigator. No QTcF prolongation was reported.

Interim analysis of Study 53718678RSV2002 in RSV-infected children ≥28 days and ≤3 years of age 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 participants and no safety signals arose in pediatric participants compared to the previously established safety profile in adults.

For the most comprehensive nonclinical and clinical information regarding JNJ-53718678, refer to the latest version of the Investigator's Brochure (IB) for JNJ-53718678.[13]

The term “study medication” throughout the protocol, refers to JNJ-53718678 or placebo.

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.

2.3. Benefit-Risk Assessment

2.3.1. Known Benefits

The potential benefit for participants participating in the observational stage of the study is to be diagnosed early with RSV, with a closer follow-up on respiratory symptoms. Even if not participating in the interventional stage, the parent(s)/caregiver(s) gets more awareness about the disease and is aware of potential risks if the infant's health condition is getting worse after diagnosis.

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 2.2). However, the clinical benefit of this compound remains to be established.

2.3.2. Potential Benefits

Subjects participating in the interventional stage of 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 participants’ return to pre-RSV health status. Results from the proposed study may be useful in developing a new antiviral therapy for RSV infection.

2.3.3. 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.

2.3.4. Potential Risks for Study Participation

All therapies have the potential to cause adverse experiences.

During completed studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, 53718678RSV1008, and 53718678RSV2001, a total of 190 participants 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 bid) for up to 13 days. Of those, 106 were healthy adult participants and 50 were healthy adult participants who were inoculated with RSV-A Memphis 37b virus. In Study 53718678RSV1003, 12 participants 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 participants received the JNJ-53718678 oral solution and the JNJ-53718678 oral suspension.

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

Please refer to Section 2.2 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.

Review of data of the TQT Study 53718678RSV1009, has identified a new important potential risk of QT prolongation for JNJ-53718678 (see Section 2.2 and the IB Addendum[14] for more information). Therefore, a change in dose regimen (see Section 4.3) and several other measures to safeguard the participants (see Section 2.3.5) 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 participants. 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 ΔΔQTcI above the threshold of 10 ms can be expected (Section 2.2).

Available clinical safety data do not indicate any safety signal or concern with regards to the cardiovascular system (Section 2.2).

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

Study procedures such as blood sampling carry a potential risk (eg, pain, discomfort, hematoma) to the participant. Therefore, minimal volumes of blood (by venipuncture or by finger or heel 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 participants while performing these assessments.

The risks of (optional) venous blood draws, finger prick, or heel stick include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and uncommonly, dizziness, nausea, and vomiting.

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 participant and is usually well tolerated, though occasionally nose bleeding can occur. Examples of other AEs that may occur, but are not considered serious, are: coughing, gagging, nausea, and vomiting; and a small amount of pain or discomfort during swabbing.

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 participant.

The collection of saliva (buccal swab) and stool are not expected to result in AEs, as these are non-invasive, patient friendly sampling procedures.

Considering the above, participation in the study does not represent a potential for serious risk to the health, safety and welfare of the parent(s)/caregiver(s) nor infant. The parent(s)/caregiver(s) will be informed that in case of emergency and/or if they have any questions regarding medical care or treatment they need to contact the treating physician during the observational stage, and the site investigator during the interventional stage directly.

Participation in the observational stage of this study will not interfere with any medical decision, such as the decision to hospitalize the infant, or with the infant's standard-of-care medical management. Participants will be treated according to the normal standard of care for their RSV infection. The decision of the parent(s)/legally acceptable representative(s) to allow or not allow the participation of the infant in the study will have no influence on any clinical decision. Based on the data entered by the parent(s)/caregiver(s), the parent(s)/caregiver(s) will be invited to perform a study visit with their infant. During that study visit (RSV-like ARI visit) a study-related rapid RSV molecular-based diagnostic assay will be performed to decide whether to initiate daily nose swab sampling over 7 more ensuing days (up to and including Day 8) for

investigation of the correlation between viral load and disease evolution. Within this time interval, in the majority of patients the RSV disease will have resolved. Study assessments will be performed in addition to, not in replacement of, standard-of-care supportive and symptomatic therapy.

2.3.5. Benefit-Risk Assessment for Study Participation

Part 1: Observational Stage

The overall risk/benefit for the observational stage of the study is acceptable, due to the limited risk related to the study procedures and sample collection, and the potential benefit related to the increased awareness of parents/caregivers of respiratory symptoms.

Part 2: Interventional Stage

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 participants (Study 53718678RSV1005) (Section 2.2);
- 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 2.2);
- No safety concerns were identified in the interim analysis of Study 53718678RSV2004 in non-hospitalized adult participants infected with RSV (Section 2.2);
- Available final data from the ongoing 53718678RSV1005 study in naturally RSV-infected pediatric participants >1 month to ≤24 months of age and from an interim analysis of Study 53718678RSV2002 in RSV-infected children ≥28 days and ≤3 years of age did not indicate safety concerns (Section 2.2);
- Several safety measures have been proposed to minimize potential risk to participants, including:
  - Only participants who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in the interventional stage of the study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of the participants in the study.
  - Utilization of study treatment discontinuation criteria and stopping criteria (see Sections 7.1 and 7.2).
  - 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 participants.

  - The establishment of an Independent Data Monitoring Committee (IDMC) to monitor data on a regular basis to ensure continuing safety of the participants enrolled in the interventional stage of the 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 infants 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 2.2, TQT Study 53718678RSV1009), the following measures have been implemented to minimize the potential risk to participants:
  - 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 4.3).
  - Specific cardiovascular and ECG-based criteria were established for eligibility assessment (see Section 5).
  - Close monitoring of the use of concomitant medications will be conducted regularly. Drugs that are moderate or strong CYP3A4 inhibitors and BCRP inhibitors will be disallowed (see Section 6.5).
  - 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 Schedule of Activities (SoA). 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 7).
  - Close monitoring of hypokalemia and hypomagnesemia and corrective actions in case of laboratory abnormalities for these analytes during the treatment period (see Section 8.5).
  - Newly administered QT prolonging drugs will be disallowed during the treatment period (see Section 6.5).
  - Specific toxicity management for cardiac and ECG related events was established (see Section 8.5).

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with participation in this study and in association with JNJ-53718678 are justified by the anticipated benefits that may be afforded to participants with RSV disease.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

Part 1: Observational Stage

The objectives applied to the observational stage are to evaluate:

- the onset and evolution of clinical symptoms of pediatric RSV disease
- the relationship between viral load and clinical symptoms at early diagnosis of pediatric RSV disease

The exploratory objectives applied to the observational stage are to evaluate:

- the characteristics of the scores that trigger a site-visit in relation to:
  - RSV diagnosis
  - the progression of clinical symptoms
  - viral kinetics
  - participation in the interventional stage
- the correspondence between disease characteristics as assessed at the site with scores as assessed by parent(s)/caregiver(s) in the RSV mobile Application (App) and Pediatric RSV Electronic Severity and Outcome Rating System (PRESORS)
- parent(s)/caregiver(s) baseline characteristics in relation to operational features such as:
  - enrollment in observational stage
  - RSV mobile App compliance
  - protocol adherence
  - enrollment in interventional stage
- the analysis of stool microbiome profiles (in optional samples) in relation to RSV disease

Part 2: Interventional Stage

Primary Objective

The primary objective is to evaluate 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 an early intervention setting in infants (≤4 months of age at enrollment) recruited from a birth cohort.

Secondary Objectives

The secondary objectives are to assess:

- the impact of treatment with 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

Exploratory Objectives

The exploratory objectives are to assess:

- the impact of baseline characteristics on antiviral activity and clinical course, including but not limited to:
  - baseline viral load
  - disease severity
  - hospitalized participants vs outpatients
  - parental history of atopy
  - randomization within 24 hours of ARI alert vs. ≥24 hours
- the relationship between the PK and antiviral activity 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 RSV infectious virus titer as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay)

3.2. Endpoints

Part 1: Observational Stage

The endpoints applied to the observational stage:

- the total score, over time, of respiratory symptoms as captured by the RSV mobile App during the pre-diagnostic phase and the post-diagnostic phase for RSV(+) participants that do not enter in the interventional stage
- the PRESORS scores by the clinician (clinician PRESORS) on the day of RSV diagnosis
- RSV viral load kinetics during the pre-diagnostic phase
- RSV viral load kinetics from Day 1 to Day 8 after RSV diagnosis over time (if not participating in the interventional stage)
- the PRESORS scores by parent(s)/caregiver(s) (parent[s]/caregiver[s] PRESORS) over time

The endpoints applied to the exploratory objectives of the observational stage are:

- the frequency and severity of individual symptoms based on the RSV mobile App, over time
- the frequency and severity of clinician recorded symptoms based on the PRESORS assessed by the investigator (clinician PRESORS) on the day of RSV diagnosis

- the individual signs and symptoms and total score that triggered the site visit
- participation in the interventional stage
- correspondence of disease characteristics as assessed by the investigator at the site and scores as assessed by parent(s)/caregiver(s)
- characteristics of parent(s)/caregiver(s) (optional) and infant at baseline in relation to (but not limited to) enrollment rate in birth cohort, RSV mobile App compliance, protocol adherence, enrollment in interventional stage

Part 2: Interventional Stage

Primary Endpoint

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

Secondary Endpoints

- virologic parameters derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs including:
  - RSV viral load and change from baseline (start of study medication) over time
  - RSV viral load AUC from immediately prior to first dose of study medication (baseline) through Day 3, Day 8, and Day 14
  - time to undetectable RSV viral load
  - proportion of participants with undetectable RSV viral load at each time point throughout the study
- clinical course related endpoints:

the following endpoints will be based on the PRESORS assessed throughout the interventional stage of 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 assessed throughout the study by parent(s)/caregiver(s) PRESORS
- change from baseline in parent(s)/caregiver(s) PRESORS (worsening or improvement)
- change from baseline in clinician PRESORS (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 participants with improvement or worsening of RSV disease based on general questions on overall health on each study day from screening till Day 21
- 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 during scheduled visits

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

- safety and tolerability, as assessed by AEs, clinical laboratory testing, ECGs, and vital signs, throughout the interventional stage of the study
- PK parameters of JNJ-53718678, as determined by popPK modeling

Exploratory Endpoints

- clinical course related endpoints:
  - in hospitalized participants:

time to age-adjusted normal values for otherwise healthy and to pre-RSV infection status for participants 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

need for and duration of noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation)

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

time to clinical stability, defined as the time from initiation of study medication 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 participants 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 participants and participants with (a) risk factor(s) for severe RSV disease

AND

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

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

- changes from baseline in the RSV F-gene sequence (and potentially other regions of the RSV genome, at the discretion of the sponsor's virologist)
- presence of pre-treatment RSV F-gene polymorphisms in relation to treatment outcome
- the occurrence of complications with onset after treatment initiation that are associated with RSV disease 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 disease per investigator assessment

- virologic parameters derived from the RSV viral load as measured by quantitative viral culture (optional, pending feasibility of performing such an assay)

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

Part 1: Observational Stage

For the observational stage no formal hypothesis will be tested.

Part 2: Investigational Stage

The primary hypothesis of this study is that JNJ-53718678 has antiviral activity against RSV as assessed by a reduction in RSV viral load AUC (from immediately prior to first dose of study medication [baseline] until Day 5) at the 5% level (one-sided) for JNJ-53718678 compared to placebo in participants recruited from a birth cohort.

4. STUDY DESIGN

4.1. Overall Design

This study is designed to assess the impact of early interception and intervention on antiviral activity and the clinical course of the disease. The study consists of 2 parts: an observational stage with a birth cohort and a Phase 2a, multicenter, randomized, double-blind, placebo-controlled interventional stage.

A target of 1,300 infants (≤4 months of age at enrollment and asymptomatic for ARI-like symptoms requiring medical intervention at the time of consent) is planned to be enrolled globally in the observational stage of this study. In the observational pre-diagnostic phase, the study aims to record early signs and symptoms of potential RSV infections and is focused on bringing the infant in for assessment at a threshold score that is based on a combination of at least one sign of upper respiratory infection, any sign of lower respiratory involvement and any sign of systemic impact (eg, feeding difficulty, disturbed sleep, disturbed activity level). All infants will be closely monitored for early signs and symptoms of RSV disease using a mobile RSV application [a] on the parent/caregiver's mobile phone (pre-diagnostic phase). For those infants with scores that cross the threshold score, an alert will be sent and they will be brought to the study site for an early diagnostic RSV test (diagnostic phase). Upon an alert, if a participant is SARS-CoV-2 positive assessed by local health practice, the participant will be withdrawn from study. RSV negative participants (RSV[-] diagnosed at site) will return to the pre-

[a] Parents/caregivers will be informed that they should not hesitate to engage their physicians on any concerns on the health status of the child as the function of the RSV mobile App is to gather study information on disease signs and to mobilize infants with a predefined set of disease signs for on-site RSV diagnosis and evaluation if the criteria for proposing intervention with the study medication are met. The mobile App is in that respect a study tool and not designed as a medical decision instrument. The caretakers should at no moment hesitate to seek medical attention with their physician if they have any concerns about the health status of the infant irrespective of their involvement with the digital monitoring system in the observation stage of the study.

diagnostic phase, and will be further closely monitored by the parent(s)/caregiver(s) through the RSV mobile App. There will be a 7-day pause in the RSV mobile App for the for the generation of alerts, after which the alert option will be switched back on. RSV positive participants (RSV[+] diagnosed at site) will be enrolled in the screening phase of the interventional stage of the study after obtaining informed consent for the interventional stage at that time. RSV(+) participants whose parent(s)/caregiver(s) do not consent for enrollment in the interventional stage and participants who are screening failures in the interventional stage will enter the post-diagnostic phase of the observational stage (hospitalized or outpatients).

The interventional stage will consist of a screening phase, a treatment phase (hospitalized or outpatients), and a posttreatment follow-up phase. It is anticipated that approximately 40 RSV(+) infants from the observational stage of the study will be enrolled in the interventional stage and will be randomized in a 1:1 ratio to receive either JNJ-53718678 or placebo bid for 7 days (14 consecutive doses). For participants 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 participants receive 14 consecutive doses in total. Antiviral activity, clinical outcomes, safety, tolerability, and PK of JNJ-53718678 in infants at early stage of an ARI due to RSV will be evaluated.

Study duration will be approximately 29 (±3) days after RSV(+) diagnosis for participants who enter the interventional stage, and 21 (±3) days after RSV(+) diagnosis for participants who do not enter the interventional stage (or 21 days [+2 weeks] in case optional stool samples will be collected [the additional time is only for optional stool sample assessments]). RSV(-) participants will be considered to have completed the study at the end of the RSV circulation. For RSV(-) participants for whom consent was given for the stool sample collection, the study ends either when the most relevant RSV surveillance data indicate that RSV is out of circulation or on the day of stool sample collection at the participant's age of 4 months (±2 weeks), whichever is last.

The enrollment period for the observational stage will be guided by local RSV epidemiological distribution and dynamics. Start and end of the RSV circulation differs by region and will be dependent on the respective country/region where the study will be conducted. The determination by the sponsor to end the study will be done on a per-site basis in line with the local seasonality pattern.

The observational stage involves nasal swabbing for RSV diagnosis, viral assessments (RSV RNA viral load), exploratory biomarker analysis, blood sampling (optional) for exploratory biomarker analyses, stool sampling (optional) for microbiome analysis, buccal swab collection (optional) for exploratory host genetic analyses, and completion of questionnaires (evaluation questionnaires and PRESORS). PRESORS can be collected on paper or in an electronic device.

In the post-diagnostic phase of the observational stage, for the RSV(+) participants whose parent(s)/caregiver(s) do not consent for enrollment in the interventional stage and participants who are screening failures in the interventional stage, the parent(s)/caregiver(s) will be asked to continue with the twice daily RSV mobile app and to also complete the PRESORS over the same period.

The interventional stage involves nasal swabbing, viral assessments (RSV RNA viral load, RSV subtype determination, and sequencing), blood sampling for PK, and completion of questionnaires (PRESORS).

An IDMC will be commissioned for this study. Refer to Committees Structure in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

The birth cohort design is intended to allow early interception and treatment when the therapeutic impact on viral proliferation as the initiator of the lung tissue damage occurs at a stage before the inflammatory response becomes the dominant driver of disease.

Blinding, Control, Study Phase/Periods, Intervention Groups

For the observational stage, a birth cohort, there will be no blinding and no treatment groups are defined. For the interventional stage a placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant 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.

DNA and Biomarker Collection

Buccal swabs will be collected (optional) for exploratory host genetic analyses. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Host genetic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the host genetic research component is to collect DNA to allow the identification of genetic factors that may influence the PK, pharmacodynamics (PD), efficacy, safety, or tolerability of JNJ-53718678 and to identify genetic factors associated with RSV disease. DNA collection is optional.

Biomarker samples (ie, blood and stool samples) will be collected to evaluate the mechanism of action of JNJ-53718678 or help to explain or predict interindividual variability in RSV disease characteristics and clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of JNJ-53718678 and aid in evaluating the intervention-clinical response relationship. Blood collection for biomarker analysis is optional.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participant's parent(s)/legally acceptable representative(s) will be fully informed of the risks and requirements of each stage of the study and, during the study, they will be given any new information that may affect their decision to continue participation of their infant. They will be told that their consent to participate 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 the infant would otherwise be entitled. Only infants whose parent(s)/legally acceptable representative(s) is/are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of each informed consent form (ICF), the term legally acceptable representative(s) refers to the legally appointed guardian of the infant with authority to authorize participation in research. For each participant, 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.

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.

4.3. Justification for Dose

The 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 C_{min} and C_{max} values within the range of the target concentrations (ie, the exposure observed in adults treated with 500 mg JNJ-53718678 qd), 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 2.2).

Based on the exposure-response analysis conducted in the TQT Study 53718678RSV1009 in healthy adult participants, 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 months of age, respectively) was selected with disallowance of comedication with moderate or strong CYP3A4 inhibitors. Based on Table 1, 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 [$paEC_{90}$]), 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 1: 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 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 (msec) (90%CI)	1.95 (0.97-3.66)	2.09 (1.08-3.98)	2.37 (1.19-4.62)
ΔΔQTcI Day 7 (msec) (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.

4.4. End of Study Definition

End of Study Definition

The end of the study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study with the determination by the sponsor to end the study taken on a per-site basis in line with the local RSV seasonality patterns. The final data from the study site (including any unshipped samples) will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site.

Study Completion Definition

An RSV(+) participant who will not enter the interventional stage will be considered to have completed the observational stage of the study if he or she has completed assessments at Day 21 (±3 days) of the observational stage. Note that the end of study will be 21 days (+2 weeks) in case optional stool samples will be collected (the additional time is only for optional stool sample assessments).

An RSV(+) participant who will enter the interventional stage will be considered to have completed the interventional stage of the study if he or she has completed assessments at Day 28 (±3 days) of the interventional stage.

An RSV(-) participant will be considered to have completed the study at the end of the RSV circulation. Start and end of the RSV circulation differs by region and will be dependent on the respective country/region where the study will be conducted. The determination by the sponsor to end the study will be done on a per-site basis in line with the local seasonality pattern.

For RSV(-) participants for whom consent was given for the stool sample collection, the study ends either when the most relevant RSV surveillance data indicate that RSV is out of circulation

or on the day of stool sample collection at the participant's age of 4 months (±2 weeks), whichever is last.

At the end of the RSV circulation, the RSV mobile App will notify the parent(s)/caregiver(s) of an RSV(-) participant and will invite them to complete evaluation questions in which, among other things, their experience using the RSV mobile App will be documented. The evaluation questionnaire from the RSV mobile App will be sent to RSV(+) participants, who did not enter the interventional stage, after completion of the last PRESORS.

5. STUDY POPULATION

Infants ≤4 months of age are eligible for enrollment in the observational stage of the study. A target of 1,300 infants is planned to be enrolled globally in this study.

The inclusion and exclusion criteria for enrolling participants in the observational stage and interventional stage of the study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.1, Sample Size Determination.

5.1. Inclusion Criteria

Part 1: Observational Stage

Each potential participant must satisfy all of the following criteria to be enrolled in the observational stage of the study:

1. The infant is ≤4 months of age at enrollment and asymptomatic for ARI-like symptoms requiring medical intervention at the time of consent to participate in the study.
2. Participant's parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative(s) must sign an ICF (observational stage) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the infant to participate in the study and is willing/able to adhere to the study procedures and assessments to be performed by the parent(s)/caregiver(s) as well as those by the investigator/site staff.
3. At least 1 parent/caregiver must be able to use the RSV mobile App at home via his/her own Android/iOS electronic device (compatible with RSV mobile App).
4. At least 1 parent/caregiver should be of legal consent age (according to local regulation).
5. The participant must have been assessed per local public health practice and considered not to have SARS-CoV-2 infection.

Part 2: Interventional Stage

Each potential participant must satisfy all of the following criteria to be enrolled in the interventional stage of the study:

1. The participant has been diagnosed with RSV infection using a rapid molecular-based diagnostic assay.
2. Participant's parent(s) (preferably both if available or as per local requirements) or their legally acceptable representative(s) has/have signed an ICF (interventional stage) indicating that he or she understands the purpose of, and procedures required for, the interventional stage of the study and is willing to allow the infant to be treated with JNJ-53718678 or placebo and is willing and able to adhere to the prohibitions and restrictions with regards to the concomitant medication (see Section 6.5), the lifestyle consideration (see Section 5.3), and study procedures and assessments to be performed by the parent(s)/caregiver(s) as well as those by the investigator/site staff.

   Refusal to give consent for the interventional stage does not exclude a participant from continued participation in the observational stage of the study.
3. The participant is at least 28 days old at the time of consent.
4. Prematurely born infant (ie, <37 weeks and 0 days of gestation at birth) is at least 3 months postnatal age at time of consent.
5. The participant weighs more than 2.4 kg.
6. The participant has an acute respiratory illness during which (s)he experienced a period of apnea,

   OR

   The participant has an acute respiratory illness with at least 1 of the signs/symptoms listed in each of the following categories at the moment of diagnosis, as evaluated by the investigator:

   - nasal congestion, rhinorrhea, pharyngitis, or otitis media; AND
   - 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 or cough; AND
   - feeding difficulties, defined as <75% intake of normal food amounts; dehydration; fever; disturbed sleep or disturbed activity level (irritable/restless/agitated/less responsive).
7. Except for the RSV-related illness, the participant 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 participant's source documents and initialed by the investigator.
8. The participant must have been assessed per local public health practice and considered not to have SARS-CoV-2 infection during this respiratory infection.

5.2. Exclusion Criteria

Part 1: Observational Stage

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

1. Inclusion in (maternal) RSV vaccine studies or RSV treatment studies.
2. During the RSV circulation, the infant is experiencing ARI-like symptoms requiring medical intervention on the day of enrollment.
3. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
4. The participant has any physical abnormality which limits the ability to collect regular nasal specimens.
5. The participant is receiving chronic home oxygen therapy at enrollment.

Part 2: Interventional Stage

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

1. The participant has major congenital anomalies or known cytogenetic or metabolic disorders other than the ones allowed below.

   Note: Isolated open ductus arteriosus and open foramen ovale are not exclusionary as these are not considered major anomalies. Participants with congenital heart disease, cystic fibrosis, congenital diaphragmatic hernia, or Down Syndrome are allowed to participate.
2. The participant is considered by the investigator to be immunocompromised, 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).
3. The participant has known or clinically suspected hepatitis B or C infection, either acute or chronic active.
4. The participant 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[13]).
5. The participant 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 medication ingestion or absorption.
6. The participant had major surgery within the 28 days prior to randomization or planned major surgery through the course of the study.

7. Criterion modified per Amendment 2.

7.1 The participant 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.

8. Criterion modified per Amendment 2.

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

9. The participant is using any disallowed medication as listed in Section 6.5.

10. The participant 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.

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

12. The participant 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 Coronavirus Disease 2019 (COVID-19) (test confirmed or suspected SARS-CoV-2 infection) within 14 days prior to randomization.

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

The required source documentation to support meeting the enrollment criteria are noted in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

The parent(s)/caregiver(s) has to complete the electronic questionnaire twice daily which takes a few minutes a day, depending on the symptoms. There are no other prohibitions or restrictions during this study, except with regards to the concomitant medication (Section 6.5).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened. Participants who do not meet the criteria for participation in the interventional stage of the study will enter the post-diagnostic phase of the observational stage (hospitalized or outpatients).

6. STUDY INTERVENTION

6.1. Study Interventions Administered

No treatment is administered in the observational stage of the study.

In the interventional stage, eligible participants will be randomized 1:1 to receive either JNJ-53718678 or placebo. Randomization should occur within 32 hours after the receipt of RSV mobile App alert. The randomization will be stratified based on the time between ARI alert and randomization (<24 hours or ≥24 hours). Study medication administration should start as soon as possible, but within 4 hours after randomization. For analysis purposes, the day of first study medication intake will be considered Day 1 for the interventional stage. Study medication will be administered bid and treatment duration will be 7 days (14 consecutive doses). Doses are based on body weight and age group. An overview of the treatments for the newly enrolled participants in the interventional stage is provided in Table 2.

Table 2: Treatment Overview

Treatment	Age Group[a]	Dosing Regimen[b,c]	Volume
JNJ-53718678	1	2.5 mg/kg bid on Days 1 to 7	A mL[d] oral suspension of JNJ-53718678
	2	3 mg/kg bid on Days 1 to 7	B mL[d] oral suspension of JNJ-53718678
	3	4.5 mg/kg bid on Days 1 to 7	C mL[d] oral suspension of JNJ-53718678
Placebo	1,2, or 3	placebo bid on Days 1 to 7	A, B, or C (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.

b. Doses are provided for JNJ-53718678-AAA.

c. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For participants 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 participants receive 14 consecutive doses in total.

d. A to C 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 body weight of the participant (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.

Note: Prior to Protocol Amendment 2, the total daily dose was the same but the daily dosing frequency was qd instead of bid.

Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM). For participants 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 participants 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 medication will be administered orally using a dosing syringe. During hospitalization, the 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.

- Hospitalized participants:
  - during hospitalization: the study medication 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 and volume administered will be recorded by the site staff.
  - after discharge: the study medication will continue to be administered at home by the parent(s)/caregiver(s) through Day 7 (or Day 8 AM, if applicable). Date and time of dosing and volume administered will be captured in the study medication log, to be completed by the parent(s)/caregiver(s).
- Participants in outpatient setting:
  - the first dose of study medication will be administered at the study site. On Day 1, date and time of dosing and volume administered will be recorded by the site staff.
  - at home, date and time of dosing and volume administered from the second dose on Day 1 through Day 7 (or Day 8 AM, if applicable) will be captured in the study medication log, to be completed by the parent(s)/caregiver(s).

Study site personnel will instruct participants' parent(s)/caregiver(s) on how to use and store the study medication for at home dosing.

If the participant vomited, regurgitated, or did not completely swallow the study medication, this information should be recorded and the participant 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 time point per the initial dosing schedule.

If participants are rehospitalized (hospitalized participants after discharge) or hospitalized (participants from outpatient setting) due to worsening of RSV disease during the treatment period, administration of study medication should continue, and the reason for hospitalization should be recorded. Every effort should be made by the investigator to perform all the assessments as indicated in the Schedule of Activities for hospitalized patients, if practically feasible.

Study medication administration must be captured in the source documents and/or the electronic case report form (eCRF).

The drug product is supplied as a 1,636-mg/bottle powder and solvent for oral suspension (G004-01 and G005, respectively). The powder will be reconstituted with the solvent to obtain a 23-mg/mL oral suspension (equivalent to 20-mg/mL oral suspension of JNJ-53718678-AAA [free form]).

The placebo drug product is supplied as a 4,068-mg/bottle powder and solvent for oral suspension (G006 and G003, respectively). The placebo powder will be reconstituted with the solvent to obtain a placebo oral suspension.

JNJ-53718678 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[13]

For a definition of study medication overdose, refer to Section 8.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study medication preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study medication received at the site is inventoried and accounted for throughout the study.

For outpatients, the dispensing of study medication to the participant, and the return of study medication from the participant (if applicable), must be documented on the study medication

accountability form. Participants' parent(s)/caregiver(s) must be instructed to return all original containers, whether empty or containing study medication.

For hospitalized patients, the study medication administered to the participant must be documented on the study medication accountability form.

All study medication will be stored and disposed of according to the sponsor's instructions. Study-site personnel and parent(s)/caregiver(s) must not combine contents of the study medication containers.

Study medication 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 medication, and study medication returned by the participant, 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 medication, or used returned study medication for destruction, will be documented on the study medication return form. When the study site is an authorized destruction unit and study medication supplies are destroyed on-site, this must also be documented on the study medication 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 study medication accountability purposes.

Study medication 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 medication will be supplied only to participants participating in the study. Returned study medication must not be dispensed again, even to the same participant. Study medication may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study medication from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions will be provided.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified based on the time between ARI alert and randomization (<24 hours or ≥24 hours). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study medication kit for the participant. The requestor must use his or her own user identification and

personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

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 participant.

Data that may potentially unblind the treatment assignment (ie, JNJ-53718678 plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the treatment code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

For participants who have had their treatment assignment unblinded, the parent(s)/caregiver(s) will be asked to continue with the participant’s remaining study visits and assessment schedule, or, at a minimum, to return with the participant to the site for a Withdrawal and a Safety Follow-up Visit.

6.4. Study Intervention Compliance

The first dose of study medication will be administered by study site personnel or by the parent/caregiver under supervision of the study site personnel. Data and time of dosing will be recorded by study staff.

Study site personnel will instruct parents/caregivers on how to use and store the study medication for home dosing.

Parents/caregivers will complete a study medication log with the date/time of study medication and volume administered.

Parents/caregivers will also be asked to record if the patient did not swallow all of the study medication or if any of the study medication was regurgitated in the study medication log.

In addition, missed doses will also be reported using the study medication log.

6.5. Concomitant Therapy

Part 1: Observational Stage

There are no prestudy or concomitant medication restrictions during the observational stage of this study. Participants may be treated according to the local standard of care. The use of medications with potential impact on RSV viral load (eg, palivizumab [Synagis®] and systemic or nasal steroids), and medications that may affect the resolution of symptoms (eg, homeopathic or naturopathic medications, bronchodilators, antibiotics, etc.) will be recorded in the eCRF from the date the ICF for the observational stage of the study is signed onwards.

Part 2: Interventional Stage

Concomitant medications, except those listed below, are allowed during the interventional stage of the study. All concomitant medications and supportive therapy different from the study medication must be recorded in the eCRF, from the date the ICF for the interventional stage of the study is signed through 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 participant into the interventional stage of the study; however, if a participant 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 participants 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 participants, 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 participants whose SpO_2 is ≥93% when clinically stable).

Participants 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.

In case antipyretics are used during the interventional stage, body temperature should be measured immediately before or >4 hours after giving antipyretics. Parent(s)/caregiver(s) 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.

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

- inhaled β-agonists or anticholinergics
- oral/IV/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.

Routine vaccinations are permitted during study participation but local guidelines should be followed.

The following medications are not permitted during the interventional stage of the study and for the indicated time period prior to screening for the interventional stage:

- 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.
- Systemic corticosteroids if used for >7 consecutive days immediately prior to randomization at doses higher than 2 mg/kg/day of prednisone or equivalent. Participants 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.
- 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 interventional stage. 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 within 14 days prior to screening for the interventional stage until 3 days after the last dose:
  - Prescription medications which are known to be a moderate or strong inhibitor of CYP3A4 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[11] 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 participant is already on a stable therapy prior to screening for the interventional stage and if the QT interval meets the eligibility criteria, however, the use of these medications cannot be initiated at screening for the interventional stage and/or during the study intervention treatment period.

- Any other investigational study medication within 30 days or 5-fold half-lives of that drug (whichever is longer) prior to screening and during the study.
- Prior exposure to JNJ-53718678 at the time of screening.
- Any investigational medical device prior to screening.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study medication must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study medication
- The participant experiences a Grade 3 rash or higher
- The participant 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 8.5)
- The participant is reported with the following laboratory abnormalities: AST or alanine transaminase (ALT) increases ≥3 × upper limit of normal (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 participant 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 participant'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 participant is withdrawn from the study before the end of the double-blind treatment period, every attempt should be made to obtain follow-up assessments.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons (for both the observational and interventional stage):

- Lost to follow-up
- Withdrawal of consent
- Death

- Participant is SARS-CoV-2 positive at any time during the study assessed by local health practice
- The participant'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 participant from the study

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

In case a participant prematurely discontinues study medication for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the participant's remaining study visits and assessment schedule, or, at a minimum, to return with the participant 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 participant's legally acceptable representative(s) withdraw consent during the treatment or follow-up phase of the interventional stage, 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 participant's parent(s)/caregiver(s) withdraw(s) the participant before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. If a participant is withdrawn from the study before the end of the double-blind treatment period, every attempt should be made to obtain follow-up assessments.

Withdrawal of Consent

A participant's parent(s)/caregiver(s) declining to return their infant for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant's parent(s)/caregiver(s) who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the original separate informed consent for optional research samples.
- Consent for optional research samples may be withdrawn, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If

requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

Consent for optional research samples may be withdrawn while the participant remains in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). 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 and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant's parent(s)/caregiver(s) repeatedly fails to return with the infant for scheduled visits and the participant's parent(s)/caregiver(s) is (are) unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant's parent(s)/caregiver(s) are deemed futile. The following actions must be taken if the participant's parent(s)/caregiver(s) fails to return with the infant to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant's parent(s)/caregiver(s) to reschedule the missed visit as soon as possible, to counsel the participant's parent(s)/caregiver(s) on the importance of maintaining the assigned visit schedule, to ascertain whether the participant's parent(s)/caregiver(s) wishes to or should continue to have the infant in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant's parent(s)/caregiver(s) (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's parent(s)/caregiver(s)'s last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant's parent(s)/caregiver(s) continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant's parent(s)/caregiver(s) to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of all measurements applicable to this study. Unscheduled visits may be performed based on the investigator's clinical judgment and may include further evaluations, as needed.

If multiple assessments are scheduled for the same timepoint, standard-of-care procedures should always take precedence over the study procedures.

In the event that an invasive procedure such as a blood draw or a mid-turbinate nasal swab is required at the same time as an assessment of clinical evaluation or vital signs or ECG, these latter assessments should be performed first.

All parental study-related assessments will ideally be performed by a single parent (or caregiver) throughout the study, if possible.

Clinical course and severity of RSV infection will be assessed through different measures (see Section 8.3.3).

In the interventional stage, 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 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 8.3.4). Sequencing results may be presented in a separate report.

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 participant's last study-related activity (see Section 8.4).

Optional blood samples and leftover mid-turbinate nasal swab samples will 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 8.11).

An IDMC will be commissioned for the interventional stage of this study. Throughout the conduct of this study, an IDMC will review unblinded safety data on a regular basis to ensure participant safety. At any point during the study, the IDMC has the authority to recommend modifications to the study conduct and/or safety assessments to the Sponsor Committee to ensure the safety of enrolled participants (see Section 9.5).

Blood Sample Collection and Handling

The maximum amount of blood drawn from each participant in the observational stage of the study will be approximately 1 mL (ICF must be signed before optional blood sampling is performed).

For the PK samples in the interventional stage, 80 µL of blood is required.

The maximum amount of blood drawn from each participant for study-specific purposes will not exceed 9.2 mL over the duration of the study in line with recommendations collated by the World Health Organization (WHO)[10], or less if per local practice guidelines. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Nasal Sample Collection and Handling

For the 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 (see Section 8.3.2). If feasible, the RSV infectious virus load may also be assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples.

The presence of viral (other than RSV) or bacterial co-pathogens will be assessed in the nasal swab sample collected at Day 1 predose by using multiplex polymerase chain reaction (PCR) at the central lab.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Details regarding the sampling procedure, storage and transportation will be provided in the Laboratory Manual. Only nasal mid-turbinate swabs provided for this study may be used. Other swabs are not acceptable for specimen collection as they may inhibit recovery of the pathogens.

Standard-of-care procedures should always take precedence over the study procedures. If a nasal sampling procedure is part of the standard of care, then the standard-of-care procedure should be performed prior to the study swabs and study swabs should be performed from the opposite nostril than that used for the standard-of-care procedure. The nasal swabs for the study will be collected in a single Universal Transport Medium (UTM) tube at time points indicated in the Schedule of Activities.

All information regarding sample preparation will be provided in the Laboratory Manual. Date and time of sample collection will be documented.

RSV is temperature-sensitive. At site, all specimens must be stored under controlled temperature conditions as indicated in the Laboratory Manual. Any mishandling of specimens should be documented and added to a Sample Collection Log.

Stool Sample Collection and Handling

Refer to the Schedule of Activities for the timing and frequency of all (optional) stool sample collections.

Stool samples for microbiome analysis will be optionally collected during the study to assess diversity and relative abundance of bacterial species (analysis upon discretion of the sponsor). Information on date and time of stool sampling as well as feeding type (liquid vs solid) and composition (eg, milk, vegetables, fruit, meat/fish) will be collected.

Stool samples can be collected at home in special dedicated sampling tubes, and shipped to the site within 30 days after sample collection. On site, samples will be stored until shipment to the sponsor or to a specialized laboratory assigned by the sponsor for microbiome analysis.

Details regarding the sampling procedure, storage and transportation will be provided in the Laboratory Manual. Only stool sample collection kits provided for this study may be used. Other collection recipients are not acceptable for specimen collection.

All samples will be shipped to the sponsor or to a central lab storage facility assigned by the sponsor following specified timing and shipping procedures and stored for a duration of at most 15 years (or according to local regulations) before being destroyed (see section on Long-Term Retention of Samples in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF

The participant's parent(s)/caregiver(s) will be provided with tools to facilitate/support participation, such as:

- Sample collection materials (nasal swabs and stool sample collection)
- Thermometer
- Nasal swab collection and storage instructions
- IP Dosing Instructions
- Parent/Caregiver information booklet
- RSV mobile App

- RSV Educational booklet

8.1. Part 1: Observational Stage

Infants who are ≤4 months of age and asymptomatic for ARI-like symptoms requiring medical intervention at the time of consent are eligible for enrollment in the observational stage of the study. Their respiratory condition will be followed before, during, and after acute RSV infection(s) and at follow-up during a single RSV epidemic circulation (as defined locally).

8.1.1. Pre-diagnostic Phase

The investigator or his/her designee will provide detailed information on the study to the participant's parent(s)/caregiver(s) and will obtain written informed consent prior to each participant's participation in the study. The ICF for the observational stage of the study will be signed before any study-related activity takes place.

After verification of the inclusion/exclusion criteria outlined in Sections 5.1 and 5.2, the participant's medical history will be reviewed and documented. Demographic and baseline characteristics will also be captured during the enrollment visit.

An optional buccal swab sample for exploratory host genetic analyses will be collected from the infant at enrollment (if consent for this optional sample is provided).

During the enrollment visit, parent(s)/caregiver(s) will be properly trained by the investigator/study site personnel to perform the nasal sampling at home. If re-training is needed, this will be performed at a later time point.

The RSV mobile App will be downloaded on the parent/caregiver's own smartphone during the enrollment visit or at any time after signing the ICF. The parent(s)/caregiver(s) will also receive a specific training on the use of the RSV mobile App.

At enrollment (+2 weeks; healthy baseline) and at the age of 4 months (±2 weeks) for participants in the observational stage, a stool sample for microbiome analysis will be optionally collected by the parent(s)/caregiver(s). If both time points fall together only 1 sample is to be collected.

Onset of Acute Respiratory Infection (ARI)

The parent(s)/caregiver(s) will observe and record the health condition of the infant at home starting from a predefined date (start date will be country and site dependent) for the entire duration of the study during a single RSV epidemic circulation. Upon activation of the RSV mobile App, pre-programmed study-related questions (App questionnaires) will be asked twice daily (morning and evening) via the parent/caregiver's smartphone. The answers of the parent(s)/caregiver(s) will drive an algorithm that calculates scores in the background of the application, where the threshold score is defined on the basis of the presence of the signs and symptoms per eligibility criteria for intervention, thus a combination of an upper and a lower respiratory sign and a sign of systemic impact. When the infant starts showing clinical signs

compatible with RSV disease that cross this threshold score in the RSV mobile App the parent(s)/caregiver(s) will receive an alert asking them to collect a nasal swab at home and to invite them to present to the site with their infant for a study visit as soon as possible, ie, within <24 hours after the receipt of the alert (RSV-like ARI visit). In addition, a notification will be sent to the study-site personnel. The RSV diagnostic test must be performed at the site during the RSV-like ARI visit as soon as possible and no later than within 24 hours after the receipt of the alert. The nasal swabs at home should preferably be taken by the same parent/caregiver and preferably also from the same nostril throughout the study (unless precluded due to bleeding). Nasal samples collected at home should be stored until the samples will be picked-up.

8.1.2. Diagnostic Phase

After the threshold score in the RSV mobile App has triggered an alert and a nasal swab has been collected at home, the parent(s)/caregiver(s) and infant will perform a study visit as soon as possible and no later than within 24 hours after the alert (Observational Stage Day 1). A second mid-turbinate nasal swab will be collected at the site by qualified study-site personnel and tested with a study-related RSV molecular-based diagnostic assay for RSV diagnosis. If the diagnostic nasal mid-turbinate sample during the RSV-like ARI visit is taken within 4 hours from the sample for testing at home, the nasal mid-turbinate swab sample during the RSV-like ARI visit should be taken from the other nostril. In that case nasal mid-turbinate swab samples should be continued to be collected from the same nostril as used during the RSV-like ARI visit. The RSV diagnostic test must be performed as soon as possible and no later than within 24 hours after the receipt of the alert. In case of an RSV(+) result, the mid-turbinate nasal swab sample collected at site will be sent to the central lab for RSV viral load determination and potentially for viral sequencing and/or viral and bacterial co-pathogen analyses. Samples from RSV(-) participants will be analyzed at the discretion of the sponsor.

Upon an alert, if a participant is SARS-CoV-2 positive assessed by local health practice, the participant will be withdrawn from study.

During the visit, a complete physical examination of all body systems, including length and head circumference and body weight measurement and skin examination will be performed.

On day of diagnosis training will be given, if applicable, on completion of the PRESORS and logs.

The parent(s)/caregiver(s) and the clinician will complete the parent(s)/caregiver(s) PRESORS and the clinician PRESORS, respectively.

Clinical assessments will be performed by the investigator or his/her designee according to routine clinical practice. Study-related information and the outcome of the complete physical examination and clinical evaluation will be captured. Depending on the outcome of the clinical evaluation, the investigator may decide to hospitalize the infant, per local standard of care. This study will not interfere with any medical decision, such as the decision to hospitalize the infant, or with the infant's standard-of-care medical management.

In case the infant has an RSV diagnosis at the site, the parent(s)/caregiver(s) will be informed on details of the interventional stage and can elect to enroll their infant in the interventional stage by completion of the informed consent process, regardless of whether the participant is hospitalized or not. RSV(+) participants whose parent(s)/caregiver(s) do not consent for participation in the interventional stage of the study and screen failures in the interventional stage will continue participation in the post-diagnostic phase of the observational stage, where nasal samples will be collected through Day 8 and the PRESORS will be completed following the same schedule as the subjects participating in the interventional stage.

Parent(s)/caregiver(s) of participants not participating in the interventional stage can still consent for the optional blood sample for exploratory biomarker analyses at the day of diagnosis in case the consent for this optional blood sample was not signed at enrollment.

An optional blood sample for exploratory biomarker analyses will be taken if consent for blood sampling is provided.

For participants that have had an ARI alert but did not enter the interventional stage of the study, an optional stool sample is to be collected at 21 days (+2 weeks) after each ARI alert unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected, if additional consent for stool sampling has been provided.

RSV negative participants (RSV[-] diagnosed at site) will continue to be further closely monitored in the observational stage. They will return to the pre-diagnostic phase and the parent(s)/caregiver(s) will continue to observe the health condition of the infant and answer the App questionnaires twice daily in the RSV mobile App until the next alert, or until the end of the RSV circulation (as determined for that site/country). There will be a 7-day pause in the RSV mobile App for the generation of alerts, after which the alert option will be switched back on. For RSV(-) participants, an optional stool sample will be collected 21 days after each ARI alert, if applicable. If for RSV(-) participants another ARI alert is triggered within a 2-week window, only 1 stool sample needs to be collected. If this second alert results in a positive RSV diagnosis, the stool sample should preferably be collected at 21 days (+2 weeks) after this RSV(+) diagnosis unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected.

8.1.3. Post-diagnostic Phase

For RSV(+) outpatients and hospitalized infants who will **NOT** be enrolled in the interventional stage of the study and for screen failures in the interventional stage a once daily mid-turbinate nasal swab will be collected from Observational Stage Day 2 until Observational Stage Day 8 at the site (for hospitalized) or at home (and at day of discharge in case hospitalized after Observational Stage Day 8). The parent(s)/caregiver(s) will complete the parent(s)/caregiver(s) PRESORS as of Observational Stage Day 2 through Observational Stage Day 14 twice daily (morning and evening). From Observational Stage Day 15 through Observational Stage Day 21, they will complete the parent(s)/caregiver(s) PRESORS once daily, in the evening.

The clinician PRESORS will be completed by the clinician for all participants on the day of diagnosis. From Observational Stage Day 2 onward it will only be completed for hospitalized patients until discharge.

Parent(s)/caregiver(s) will continue completion of the App questionnaires until Day 21 (end-of-study).

For participants who did not enter the interventional stage of the study, an optional stool sample is to be collected 21 days (+2 weeks) after the ARI alert unless this time point coincides (±2 weeks) with the participant's age of 4 months; in that case only 1 sample is to be collected.

8.2. Part 2: Interventional Stage

Participants with diagnosed RSV infection (RSV[+]) at site will be enrolled in the screening phase of the interventional stage of the study after obtaining informed consent for the interventional stage at that time.

8.2.1. Screening Phase

The procedures to ensure the eligibility of the participant for the interventional stage of the study will only be performed after the parent(s)/caregiver(s) have given their written informed consent. At the time of consent, the participants should be at least 28 days old or at least 3 months postnatal age for prematurely born infants (ie, <37 weeks and 0 days of gestation at birth) to be eligible for enrollment in the interventional stage of the study.

If needed, and depending on the time of presentation, screening/predose assessments can continue the next calendar day, in which case the first study medication intake will be on that day, immediately after establishing eligibility. A predose mid-turbinate nasal swab should be collected as close as possible and within 8 hours prior to the first administration of study medication. The mid-turbinate nasal swab sample collected at site will be sent to the central lab for RSV viral load determination and potentially for viral sequencing and/or viral and bacterial co-pathogen analyses. If the RSV-like ARI visit nasal swab taken at the site was taken less than 8 hours prior to start of dosing, then this sample can be used as the Day 1 predose sample, and no additional nasal sample needs to be collected at Day 1 predose.

8.2.2. Double-blind Treatment Phase

On Day 1, eligible participants will be randomized in a 1:1 ratio to receive either JNJ-53718678 or placebo. A participant needs to be randomized within 32 hours after the receipt of the RSV mobile App alert. The randomization will be stratified based on the time between ARI alert and randomization (<24 hours or ≥24 hours). Study medication administration should start as soon as possible, but within 4 hours after randomization.

Study medication will be administered bid for 7 days (14 consecutive doses). For participants 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 participants receive 14 consecutive doses in total. The doses to be administered are based on body weight and age group (see Table 2). For

hospitalized participants, the study medication will be administered by study site personnel or by the parent(s)/caregiver(s) under supervision of the study site personnel during hospitalization. In outpatients, the first dose of study medication will be administered at the study site. All participants will receive standard supportive care for RSV infection as per local standard of care considering the disallowed medication provided in Section 6.5.

Hospitalized participants 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). After discharge, the discharged participants will follow the same visit schedule as outpatients.

For hospitalized participants after discharge and for outpatients, some of the assessments will be performed during on-site visits (Day 3, 5 and 8). These scheduled study visits, if feasible for the study site and if allowed per local regulations, can also be done as home visits.

Pharmacokinetic assessments during the study will be based on sparse sampling (on Day 1 approximately 1 hour after administration of study drug [after the ECGs are obtained] and on Day 3 or Day 5 at least 4 hours after the AM and prior to the PM dosing) and will be performed using a popPK model (see Section 8.8).

Investigational staff will review daily the completion of the parent(s)/caregiver(s) PRESORS and the logs. The investigational staff will contact the parent(s)/caregiver(s) in case of incompliance.

8.2.3. Follow-up Phase

Participants will be evaluated for a total of approximately 28 (±3) days post randomization (Days 9 to 28 [±3]).

Both outpatients and hospitalized patients after discharge will be asked to return to the site for follow-up assessments as an outpatient on Day 14 and Day 21. If feasible for the study site and if allowed per local regulations, these visits can also be done as home visits. On Day 28 (±3), participant's parent(s)/caregiver(s) will be contacted by the site staff for a telephone follow-up visit. In case a participant 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 participant 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.

The parent(s)/caregiver(s) will complete the parent(s)/caregiver(s) PRESORS as of Day 9 through Day 14 bid (morning and evening). 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.

8.2.4. Withdrawal and Safety Follow-up Visits

In case a participant prematurely discontinues study medication treatment for any reason (except withdrawal of consent), the parent(s)/caregiver(s) will be asked to continue with the participant's remaining study visits and assessment schedule, or, at a minimum, to return with the participant 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 participant'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 Schedule of Activities.

8.3. Viral Kinetics and Clinical Outcome

8.3.1. Viral Load Kinetics (Observational Stage)

Mid-turbinate swab specimens for the determination of RSV viral load will be collected at the time points indicated in the Schedule of Activities. 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). Date and time of sampling should be recorded for all participants. If the diagnostic nasal mid-turbinate sample during the RSV-like ARI visit is taken within 4 hours from the sample for testing at home, the nasal mid-turbinate swab sample during the RSV-like ARI visit should be taken from the other nostril. In that case nasal mid-turbinate swab samples should be continued to be collected from the same nostril as used during the RSV-like ARI visit.

For participants with diagnosed RSV infection who do **NOT** participate in the interventional stage of the study and for screen failures, nasal swabs will be collected once daily through Observational Stage Day 8 and nasal swab collection will stop after Observational Stage Day 8 regardless of hospitalized or outpatient status. For RSV(+) patients who are hospitalized after Observational Stage Day 8 one additional nasal swab will be collected at day of discharge.

8.3.2. Antiviral Activity (Interventional Stage)

The mid-turbinate nasal swab on Day 1 should be collected as close as possible prior to the first administration of study medication. If the RSV-like ARI visit nasal swab taken at the site was taken less than 8 hours prior to start of dosing, then this sample can be used as the Day 1 predose sample, and no additional nasal sample needs to be collected at Day 1 predose. The next nasal swabs should be collected preferably at approximately the same time as the predose swab taken on Day 1 and preferably prior to dose administration.

For participants with diagnosed RSV infection who participate in the interventional stage of the study, nasal swabs will be collected daily through Day 8 in all participants. As of Day 8, in participants who were symptomatic based on clinician PRESORS at Day 8, daily nasal swabs will be collected through Day 13 or until the participant becomes asymptomatic based on the

parent(s)/caregiver(s) PRESORS, as evaluated by the investigational staff (whichever comes first). For hospitalized patients, nasal swabs will be collected each day during hospitalization through Day 13 or until discharge (whichever comes first). On Day 14 and Day 21, a nasal swab will be collected during the scheduled visit for all participants (outpatient or hospitalized).

For hospitalized participants daily during hospitalization and for outpatients at scheduled visits, mid-turbinate nasal swabs will be collected by a healthcare professional (HCP; investigator/study site personnel). On days when no visit is scheduled, mid-turbinate swabs are collected at home by the parent(s)/caregiver(s). All mid-turbinate swabbing may also be performed at the site if this is preferred by the parent(s)/caregiver(s).

All parent(s)/caregiver(s) 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 at home. All nasal swabs collected at home should be stored until the samples will be picked-up. Additional information about the collection, handling, and shipment of biologic samples can be found in the laboratory manual.

For the evaluation of antiviral activity, the RSV viral load in nasal secretions will be measured at the central laboratory using a qRT-PCR assay on mid-turbinate nasal swab specimens. If feasible, the RSV infectious titer may also be assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples.

8.3.3. Clinical Course of RSV Infection

The study will include the following evaluations of the clinical course of RSV infection for all RSV(+) participants (hospitalized or outpatients) during either the post-diagnostic phase of the observational stage (for those who do not enter the interventional stage or are screen failure in the interventional stage) or the interventional stage of the study:

- Hospitalized patients and participants in outpatient setting:
  - clinical parameters: respiratory rate, heart rate, SpO_2, and body temperature as measured by the investigator during scheduled visits
  - body temperature as measured by the parent(s)/caregiver(s) and recorded in the temperature log (for outpatients and after discharge of hospitalized patients)
  - 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 by the investigator (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

- Hospitalized patients 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, translational 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.

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

The parent(s)/caregiver(s) PRESORS assessment should be completed once at predose, then twice daily (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 the Schedule of Activities). The first parent(s)/caregiver(s) PRESORS of the twice daily schedule on Day 1 needs to be completed within 4 hours before randomization, or if done after randomization, as close as feasible and prior to the first administration of study medication.

8.3.4. Viral Sequencing

In the interventional part, 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 presence of baseline RSV F-gene polymorphisms on the antiviral response will be explored. Sequencing results may be presented in a separate report. Sequencing data will not be reported to the investigators.

In the observational part, viral sequencing may be performed as an exploratory analysis.

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

8.4. Safety Assessments

Part 1: Observational Stage

For the observational stage of the study neither changes in ongoing therapy will be imposed through participation in this study, nor any investigational medicinal product will be

administered. Hence, the overall safety of the participants in the observational stage will not be assessed, but safety information related to study-specific procedures will be collected and recorded throughout the observational stage. All serious and non-serious AEs related to the study sampling procedures and all deaths (including their causality) will be documented from signing of the ICF allowing inclusion in the observational stage onwards and will be communicated according to the sponsor's procedure.

Part 2: Interventional Stage

Safety and tolerability will be evaluated throughout the interventional stage, ie, from signing of the ICF allowing inclusion in the interventional stage onwards until the last study-related activity. The following evaluation of safety and tolerability will be included:

- Adverse events
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Clinical laboratory tests (local)

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

AEs will be reported and followed by the investigator as specified in Section 8.6, Adverse Events and Serious Adverse Events and Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.4.1. Physical Examinations

To evaluate the participant's eligibility, a complete physical examination of all body systems, including length and head circumference and body weight measurement and skin examination will be performed at the day of RSV diagnosis.

A directed physical examination will be performed at several time points throughout the study (see Schedule of Activities). A directed physical examination 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 participant develops a cutaneous reaction/rash, vaginal and rectal exams may be done if clinically relevant.

To obtain the actual body weight, participants 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 participant.

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

8.4.2. Vital Signs (Blood Pressure)

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

Blood pressure will be assessed supine only 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.

8.4.3. Electrocardiograms

Screening and on-treatment ECGs will be collected at the time points indicated in the Schedule of Activities.

Electrocardiograms (triplicate 12-lead ECG) should be performed using procedures commensurate with the participant'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 participant 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 5.2), the participant 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 participant'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 participant has a QTcF interval ≥500 ms based on the 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 participant needs to be withdrawn from study intervention (see also Sections 8.5 and 7.1). In case other clinically relevant ECG abnormalities are observed post start of study intervention, 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.

8.4.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.5. Specific Toxicities and Safety Topics of Special Interest

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

AST and ALT Elevation

Management will be at the discretion of the investigator and should follow generally accepted medical standards. Grading of AST and ALT elevation will be based on the DMID Pediatric Toxicity Table (see Appendix 5).

For Grade 3 or 4 laboratory abnormalities, participants 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)

Participants may continue the intake of study medication.

Participants 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, participants will permanently discontinue the intake of study medication, although with continuation of appropriate safety follow-up visits.

It is recommended that the investigator contacts the sponsor to discuss the case. Participants 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 participant's study intervention must be discontinued if the participant has a QTc value ≥500 ms at any scheduled visit based on the machine read ECG result (mean of triplicate), confirmed by repeat ECG recording during the same visit day (see Section 7.1). For participants 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 local laboratory.
- If hypokalemia or hypomagnesemia is identified, the levels of potassium and/or magnesium should be checked as soon as possible and corrected to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values) is required.
- An ECG should be repeated every 24 hours until resolution of QTc interval prolongation is confirmed. The participant’s condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled assessments/visits.

8.6. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study depending on the stage of the study (see Section 8.6.1).

Special attention will be paid to those participants 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.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints (PQCs), refer to Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

For the observational stage of the study only all serious and non-serious AE's related to study sampling procedures and all deaths will be reported from the time a signed and dated ICF for the observational stage is obtained until completion of the participant's last study-related procedure in the observational stage.

For the interventional stage of the study, all AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF for the interventional stage is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study medication, and all deaths must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

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

During the observational stage, all deaths including causality must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event as an SAE.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, 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 an SAE should be transmitted electronically.

8.6.2. Follow-up of Adverse Events and Serious Adverse Events

AEs will be followed by the investigator as specified in Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.6.3. Regulatory Reporting Requirements for Serious Adverse Events

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). 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.

8.7. Treatment of Overdose

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

The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until JNJ-53718678 can no longer be detected systemically.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.8. Pharmacokinetics

Pharmacokinetics are only applicable to the interventional stage of this study.

For newly recruited participants in the interventional stage, a blood sample for determination of JNJ-53718678 concentrations will be collected through finger prick or heel stick approximately 1 hour after administration of study drug (after the ECGs are obtained) on Day 1 and at least 4 hours after the AM and prior to the PM dosing on Day 3 or Day 5.

The following times need to be recorded: date and time of study medication intake, date and time of PK blood sampling, and time of meal if any in the time window of 30 minutes before and 30 minutes after study medication intake on the day of PK sampling.

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

8.8.1. Evaluations

Samples will be used for determination of JNJ-53718678 concentrations. Samples can also be used for the analysis of metabolites of JNJ-53718678, protein binding, 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 participant confidentiality will be maintained.

8.8.2. Analytical Procedures

Samples will be analyzed (applicable treatment group only [not the placebo group]) to determine concentrations of JNJ-53718678 using a validated, specific and sensitive method under the supervision of the sponsor.

8.8.3. Pharmacokinetic Parameters and Evaluations

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. This model will be used to derive the individual PK parameters. 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, gender, creatinine clearance, 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 the analytes in scope. If deemed useful to evaluate the safety or efficacy of JNJ-53718678, popPK modeling of other analytes (eg, excipients) may be performed at the discretion of the sponsor.

8.9. Pharmacokinetic/Pharmacodynamic Evaluations

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

8.10. Host Genetic Research

In the observational stage, a buccal swab will be collected from participants who consent separately to this component of the study to allow for exploratory host genetic variation analysis (DNA) (where local regulations permit).

Details regarding the handling, storage and transfer procedures will be provided in the Laboratory Manual.

Participant participation in host genetic research component of the study is optional.

Host genetic analyses may be conducted at the sponsor's discretion and reported separately from this study.

8.11. Biomarkers

Stool samples for microbiome analysis will be optionally collected during the study to assess diversity and relative abundance of bacterial species (analysis upon discretion of the sponsor).

In the observational stage, optional blood samples will be used for exploratory biomarker analyses (eg, proteins, RNA, immune cell populations), on the premise that these analyses investigate the role of biomarkers in RSV-related disease.

Leftover mid-turbinate nasal swab samples from samples collected during the study may also be used for exploratory biomarker analyses (eg, proteins, RNA, immune cells, microbiome).

Details regarding the handling, storage and transfer procedures will be provided in the Laboratory Manual.

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

8.12. Other Evaluations

In the interventional stage, the presence of viral (other than RSV) or bacterial co-pathogens will be assessed in the nasal swab sample collected at baseline (Day 1 predose) by using multiplex PCR at the central lab.

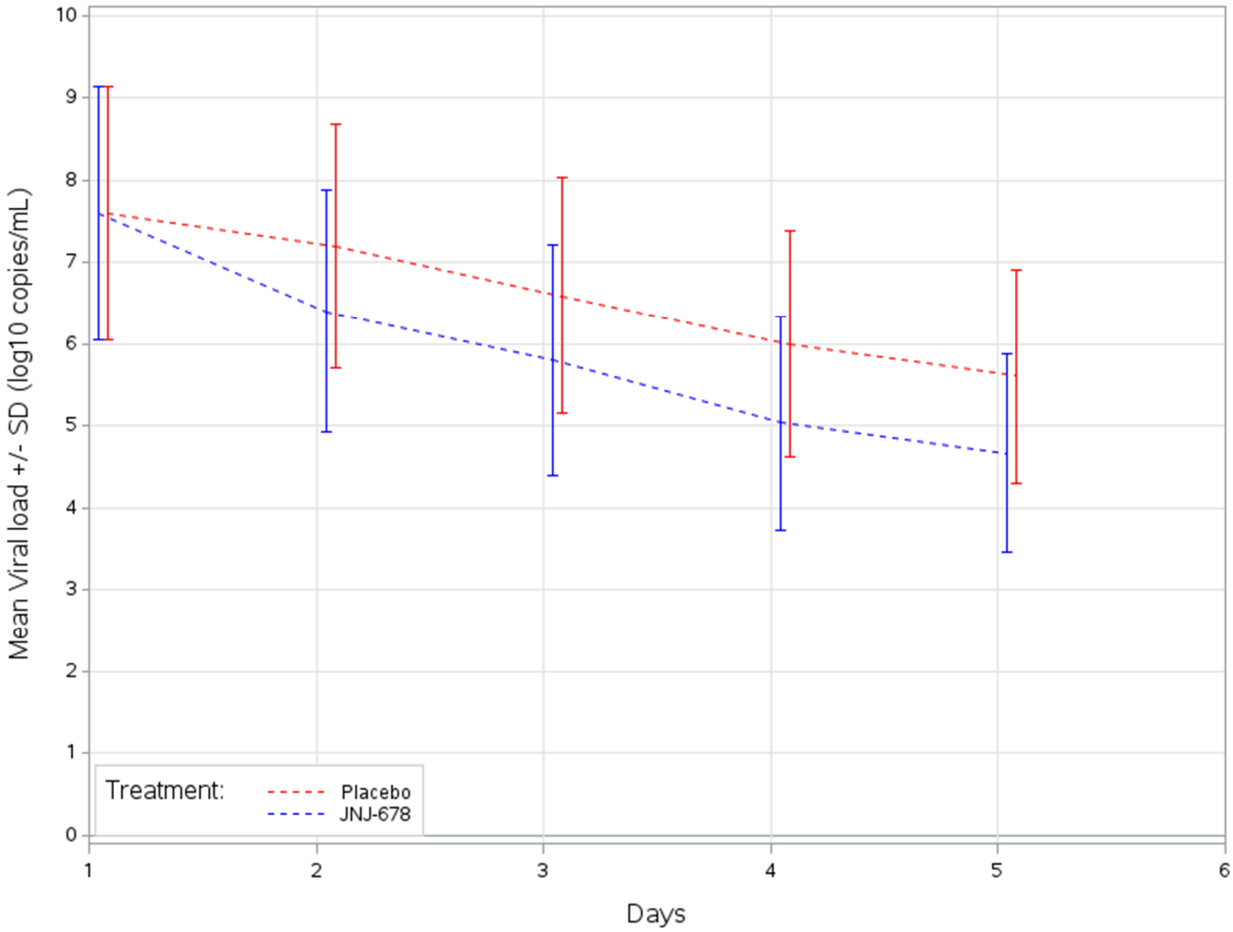
9. STATISTICAL CONSIDERATIONS

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 (SAP).

9.1. Sample Size Determination

The sample size of the interventional stage is based on results obtained in an earlier birth cohort study (Janssen R&D, data on file) and the specified analysis method using simulated data. Based on 10,000 simulated datasets of 40 participants, with an assumed 10% drop-out rate and an effect size of early treatment of 0.75 $\log_{10}$ copies.day/mL reduction in viral load versus placebo on average (as illustrated in Figure 2), there is a power of 88% to reject the null hypothesis of no antiviral effect of JNJ-53718678 treatment using a significance level of 5% (one-sided).

Figure 2: Illustration of Viral Load over Time by Treatment Assumed in the Sample Size Calculation



The sample size of the birth cohort is based on the sample size required for the interventional stage. It is assumed based on the results of a previous observational birth cohort study (Janssen R&D, data on file) that approximately 10% of the infants participating in the birth cohort will be diagnosed as RSV(+) and will develop ARI disease signs compatible with a minimum disease severity threshold for intervention.

At the stage of the temporary hold of the interventional stage of the study on 2 March 2020, 862 infants were enrolled in the birth cohort, leading to 29 infants who were diagnosed as RSV(+) and 20 infants who participated in the interventional stage. The incidence of RSV(+) was lower than anticipated, which for a large part may be explained by the relatively late in the RSV season start of recruitment for the first participating country in the study (Panama). It is assumed that when recruitment into the birth cohort is re-initiated in time for the next season, ~10% of participants will be diagnosed as RSV(+). In order to maintain the target of 40 participants in the interventional part, the maximum number of infants that may be recruited in the birth cohort is set at 1,300. With an additional 438 participants in the birth cohort, an assumption of 10% incidence of RSV(+) and a 50% rate of infants who will enter the interventional stage, the target of 40 participants in the interventional stage is expected to be reached.

As the sample size of the 2 parts are linked and assumptions have to be made on the percentages of RSV(+) and eligibility, the study may continue at the discretion of the sponsor when more than 40 participants are included in the interventional stage (with a maximum of 60) and may also be considered completed if at least 32 infants have been included in the interventional part.

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 3: Populations for Analyses

Part	Population	Description
Observational Stage (Part 1)	$Enrolled_{obs}$	All participants who signed the ICF of the observational stage
	$ARI\ visit_{obs}$	All participants who had at least one ARI-visit at the site
	$RSV(+)_{obs}$	All participants who were diagnosed RSV positive based on the study-related RSV molecular-based diagnostic assay during an ARI-visit at the site
	$Safety_{obs}$	All participants who had at least one swab or blood draw
Interventional Stage (Part 2)	Enrolled	All participants who signed the ICF of the interventional stage
	Randomized	All participants who were randomized in the interventional stage of the study
	ITT	All participants who were randomized in the interventional stage and who took at least 1 dose of study medication
	ITT-i	All participants who were in the ITT population and who were infected with the RSV virus and who had a centrally confirmed RSV infection with an RSV viral load of ≥ 1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) at baseline
	PK-evaluable	All participants who took at least 1 dose of JNJ-53718678 and for whom the Day 3 sample was evaluable
	Safety	All participants who took at least 1 dose of study medication

9.3. Statistical Analyses

9.3.1. Participant Information

Participant characteristics will be summarized for the observational stage and interventional stage separately and by population. Parent/caregiver characteristics will also be summarized.

For the interventional part, all demographic (eg, age, length, weight, race, gender), other initial participant characteristics (physical examination, medical and surgical history, family history, concomitant diseases), RSV disease characteristics (eg, subtype, time since symptom onset, age at RSV[+]) will be tabulated and analyzed descriptively by treatment group and overall, by population (if applicable).

9.3.2. Analyses Specific to the Observational Stage

For all participants of the observational stage that reached the threshold for an ARI-alert, the onset and evolution of clinical symptoms of pediatric RSV disease will be analyzed descriptively. The signs and symptoms that are captured in the RSV mobile App and by the investigator will be compared for those that were diagnosed RSV(-) and RSV(+) (for participants that performed an ARI visit). For participants that were RSV(+), the viral load will be summarized over time, and viral load will be correlated with disease characteristics as captured on the RSV mobile App and as measured at the site.

For the exploratory endpoints a key variable is the score that triggered the site visit. It will be investigated if the RSV mobile App data and other characteristics can predict this score. The score itself (and its components) will be used correlate to subsequent parameters such as RSV diagnosis (positive/negative), disease progression, viral kinetics, and participation in the interventional stage.

To investigate the feasibility of the birth cohort to provide an early diagnosis of RSV, characteristics of parent(s)/caregiver(s) will be correlated to components such as (but not limited to) RSV mobile App compliance, protocol adherence (eg, site visits), participation in interventional stage, randomization within 24 hours of alert. Correspondence of disease assessment across parent(s)/caregiver(s) and site will be investigated over time.

For the analysis of viral load kinetics during the observational stage, refer to Section 9.3.3.1.

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

9.3.3. Viral Kinetics and Clinical Outcome Analyses

Details regarding the analyses will be described in the SAP.

9.3.3.1. Viral Load Kinetics (Observational Stage)

Viral load kinetics will be determined based on measurements of RSV viral load in nasal secretions by a qRT-PCR assay on mid-turbinate nasal swab specimens. These data will be analyzed descriptively and graphically. For the RSV viral load assessed before the day of RSV diagnosis and at the diagnosis itself it will be investigated if the signs and symptoms observed and captured previous to these RSV viral load assessments have predictive value for the absence or presence of the virus as well as for the key characteristics of the viral load (eg, peak viral load), when virus is present. The correspondence between viral load and signs and symptoms will be investigated graphically by visualizing the viral load and signs and symptoms together over a period of time before and after RSV diagnosis. Exploratory analyses and details will be described in the SAP.

9.3.3.2. Antiviral Activity (Interventional Stage)

Viral load kinetics will be determined based on measurements of RSV viral load in nasal secretions by a qRT-PCR assay on mid-turbinate nasal swab specimens. These data will be analyzed graphically and descriptively. Kaplan-Meier Curves will be produced to describe the time to event data. The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized participants who received at least one dose of study medication and who have a centrally confirmed RSV infection with an RSV viral load of $\geq$1 $\log_{10}$ copies/mL above the lower limit of quantification (LLOQ) at baseline.

The primary efficacy endpoint is the RSV viral load AUC from immediately prior to first dose of study medication through Day 5 ($AUC_{1\text{-}5\ days}$) derived from the RSV viral load as measured by a qRT-PCR assay in nasal swabs. Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood-based repeated measures approach. Analyses will include the

fixed, categorical effects of treatment, stratum (time from ARI alert within 24 hours or outside 24 hours), 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. Differences between treatment groups in viral load for time points, and the difference in the $AUC_{1\text{-}5\ days}$ between treatment groups will be derived using appropriate contrasts deriving least square mean differences, including the 90% 2-sided confidence intervals. The primary null hypothesis of worse or no treatment effect will be rejected if the viral load $AUC_{1\text{-}5\ days}$ is significantly lower than placebo using a one-sided test at the 0.05 significance level.

9.3.3.3. Clinical Course of RSV Infection

Endpoints related to evaluation of the clinical course of RSV infection will be analyzed graphically and descriptively. Both scores from the RSV mobile App as well as PRESORS scores will be summarized descriptively over time and may be modeled using longitudinal analysis. Relationship between symptoms reported on the RSV mobile App and becoming RSV(+) (versus RSV[-]), and need for hospitalization (versus outpatient) will be investigated graphically. Also, correlation between symptoms reported on the RSV mobile App as predictive of viral load characteristics will be investigated, as well as correlation between signs and symptoms and viral load over time. Time-to variables will be analyzed using Kaplan-Meier plots. For the interventional stage these might be modeled using an accelerated failure time model, adjusted for covariates, such as stratum and baseline viral load, to estimate differences between treatment groups. Endpoints related to hospital stay will be explored.

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

9.3.3.4. Correlation Between Antiviral Effect and Clinical Course Endpoints

Selected antiviral effect and selected clinical course endpoints (eg, RSV mobile App scores and PRESORS symptoms and total score) will be subjected to correlation analysis. Various approaches, including graphical analysis will be used, and data may be modeled using joint analysis and structural equation modeling.

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

9.3.3.5. Viral Sequencing

The results of viral sequencing will be evaluated by the sponsor's virologist. Pre-treatment polymorphisms and relevant post-baseline changes in the RSV F-gene (and other regions of the RSV genome, if applicable and on request of the sponsor's virologist) will be tabulated and described. The effect of pre-treatment RSV F-gene polymorphisms and relevant post-baseline RSV F-gene changes on antiviral response and/or clinical outcomes will be explored.

9.3.4. Safety Analyses

For safety analyses a distinction will be made between the observational stage and the interventional stage. For the observational stage all data will be summarized descriptively for all participants enrolled.

For the interventional stage a separate analysis will be performed.

All safety analyses will be made on the Safety Population as defined in Table 3.

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 AEs with onset during the interventional stage 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 participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data.

The laboratory abnormalities will be determined per the criteria specified in the DMID Pediatric Toxicity Tables (version November 2007) and in accordance with the normal ranges of the clinical laboratory if no DMID gradings are available.

Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

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

A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

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 (the predose ECG will be used as baseline).

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QTcB and QTcF.[12]

Frequency tabulations by treatment group of the abnormalities will be made.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Descriptive statistics of actual values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically relevant limits (as defined in the SAP) will be summarized.

Physical Examinations

Clinically relevant findings resulting from the physical examination will be reported as AEs.

9.3.5. Other Analyses

9.3.5.1. Pharmacokinetic Analyses

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

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 participant characteristics (demographics, laboratory variables, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a popPK analysis plan and the results of the popPK 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 popPK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a popPK re-analysis when they become available after database lock.

Data will be listed for all participants with available whole blood concentrations. Participants 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 medication; 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 participants and samples excluded from the analysis will be clearly documented in the study report.

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.

9.3.5.2. Pharmacokinetic/Pharmacodynamic Analyses

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.

9.3.5.3. Host Genetic Analyses

DNA samples will be used for research related to RSV disease susceptibility or severity. Genomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome in relation to RSV.

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

9.3.5.4. Biomarkers Analyses

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

9.3.5.5. Other Analyses

Data from the viral (other than RSV) and bacterial co-pathogen testing at baseline (Day 1 predose) in the interventional stage will be listed and tabulated.

9.4. Interim Analysis

No formal interim analysis has been planned.

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.

In case of an interim analysis, investigators, participants' parents/caregivers, and local sponsor representatives will remain blinded. The sponsor leadership team responsible for decisions and the central study team required to generate and interpret results will have access to unblinded data.

9.5. Independent Data Monitoring Committee

An IDMC, will be established as noted in Committees Structure in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

The IDMC will be established to monitor and review data for the interventional stage in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this stage. The committee will meet periodically to review safety data. 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 participants.

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. 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 recommendations, and will communicate these decisions to the study team. Details are provided in the IDMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse event
ALT	alanine transaminase
App	application
aPTT	activated partial thromboplastin time
ARC	Anticipated Event Review Committee
ARI	acute respiratory infection
AST	aspartate aminotransferase
AUC	area under the RSV viral load-time curve
$AUC_{0\text{-}xh}$	AUC from time of administration up to time x,
$AUC_{0\text{-}\infty}$	AUC from time of administration extrapolated to infinity
$AUC_{1\text{-}5\ days}$	AUC from immediately prior to first dose of study medication through Day 5
BALF	bronchoalveolar lavage fluid
BCRP	breast cancer resistance protein
bid	twice daily
BM	bone marrow
BW	body weight
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
C_{trough}	predose plasma concentration
CYP	Cytochrome P450
DMID	Division of Microbiology and Infectious Diseases
EC_{50}	effective concentration for 50% inhibition
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
eDC	electronic data capture
FC	food consumption
GCP	Good Clinical Practice
GGT	γ-glutamyltransferase
GLP	Good Laboratory Practice
HCP	healthcare professional
hERG	human-ether-a-gogo-related
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	50% inhibition concentration
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
I_{Kr}	cardiac potassium membrane current
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LLOQ	lower limit of quantification
LRTI	lower respiratory tract infection
MATE	multidrug and toxin extrusion

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)
P-gP	P-glycoprotein
PK	pharmacokinetic(s)
PND	post-natal day
popPK	population pharmacokinetic(s)
PQC	Product Quality Complaint
PRESORS	Pediatric RSV Electronic Severity and Outcome Rating Systems
PT	prothrombin time
q24h	every 24 hours
qd	once daily
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RBC	red blood cell
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent AE
t_{max}	time to reach maximum plasma concentration
TQT	thorough QT
TR	total radioactivity
UGT	glucuronyl transferase
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local 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

  Note: In case of hypokalemia and/or hypomagnesemia at screening or Day 8, the levels of potassium and/or magnesium should be checked as soon as possible and corrected to prevent cardiac disturbances.

- Estimated glomerular filtration rate (eGFR) will be calculated/reported by the local 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 as per the Schedule of Activities (SoA). If dipstick is abnormal, microscopic evaluation should be performed, with evaluation of sediment as listed above. In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory and need to be captured in the eCRF.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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.

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.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study medication 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, participant 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 participant:

- 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

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 participant's parent[s]/legally acceptable representative[s])
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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.

Approval for the collection of optional samples for research and for the corresponding ICFs must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants 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 AEs that are serious, unlisted/unexpected, and associated with the study medication
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants

- Report of deaths of participants 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 participants, 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.

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 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

INFORMED CONSENT PROCESS

Each participant’s parent(s)/legally acceptable representative(s) 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 participant’s parent(s)/legally acceptable representative(s) 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 potential participant’s parent(s)/legally acceptable representative(s) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. The participant’s parent(s)/legally acceptable representative(s) will be informed that the infant’s participation in the study is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate or to withdraw from the study will not affect the care the infant will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a

participant 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 infant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant's parent(s)/legally acceptable representative(s) is/are authorizing such access.

The participant's parent(s)/legally acceptable representative(s) 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 participant's parent(s)/legally acceptable representative(s) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant's parent(s)/legally acceptable representative(s).

Participant's parent(s)/legally acceptable representative(s) will be asked for consent to provide optional samples for research where local regulations permit. After informed consent for the study is appropriately obtained, the participant's parent(s)/legally acceptable representative(s) will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant's parent(s)/legally acceptable representative(s).

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. No personal data (eg, no phone number, e-mail, first/last name, mac address,…) will be stored.

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 participants confidential.

The informed consent obtained from the participant's parent(s) (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to the infant's 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 participant's parent(s)/legally acceptable representative(s) has/have the right to request through the investigator access to the infant's 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 DNA and biomarker research is not conducted under standards appropriate for the return of data to participants. 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 participants 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.

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 scientific and exploratory DNA and biomarker research if the participant's parent(s)/legally acceptable representative(s) consent. Samples will only be used to understand RSV disease. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Independent Data Monitoring Committee

The IDMC will be established to monitor and review data for the interventional stage in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this stage. The committee will meet periodically to review safety data. 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 participants.

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. 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 recommendations, and will communicate these decisions to the study team. Details are provided in the IDMC Charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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, including host genetic and exploratory biomarker research 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 host genetic and exploratory biomarker 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 participant 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 (ICMJE) 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 sub-study 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 of the availability of the final data (tables, listings, graphs), 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. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

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, and direct transmission of clinical laboratory data from a central laboratory (if applicable) and the data transmitted by the participants mobile phone into the sponsor's data base. 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.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. 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 participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative 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 a query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

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: participant 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 AEs and follow-up of AEs; concomitant medication; study medication receipt/dispensing/return records; study medication administration information; and date of study completion and reason for early discontinuation of study medication 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).

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 study-specific data fields as determined by the protocol. These data are 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. The following data will be recorded directly on the electronic device and will be considered source data: clinician PRESORS and parent(s)/caregiver(s) PRESORS, medication, nasal swabs, and temperature logs.

MONITORING

The sponsor will use a combination of monitoring techniques to monitor this study.

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, and physician's office medical records); a sample may be reviewed. 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

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. Participant 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.

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 participant, 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.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

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 participants by the investigator
- Discontinuation of further JNJ-53718678 development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study medication. An AE 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 AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.6.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union (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 participant 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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 Study Medication

An AE is considered associated with the use of the study medication if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the study medication.

Doubtful

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

Possible

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

Probable

An AE that might be due to the use of the study medication. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(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 treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade 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 participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

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

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

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

PROCEDURES

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study depending on the stage of the study (see Section 8.6.1).

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study medication, 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.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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 personnel only)

- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 medication or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant 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 an SAE.

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

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study within the study duration of the last dose of study medication, whether or not the event is expected or associated with the study medication, is considered an SAE.

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.

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 participants, 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.

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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.6.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

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.

10.5. Appendix 5: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007, draft)

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal
Rx = Therapy
Mod = Moderate
ADL = Activities of Daily Living
LLN = Lower Limit of Normal
Req = Required
IV = Intravenous
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, National Cancer Institute's [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

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

(Older than 3 months of age)

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

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

(Older than 3 months of age)

PERIPHERAL NERVOUS SYSTEM				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuropathy/ Lower Motor Neuropathy	-	Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in "stocking glove" distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness.
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2 x ULN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation (<2 x ULN)	Proximal muscle weakness and/or atrophy affecting motor function +/- CPK elevation; or severe myalgias with CPK >2 x ULN;	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms

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

(Older than 3 months of age)

OTHER				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)	-	38.5 - 40.0°C 101.3 – 104.0 °F	Greater than 40.0°C Greater than 104.0°F	Sustained Fever: Equal or greater than 40.0°C (104.0°F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty swallowing, but able to eat and drink	Painful: unable to swallow solids	Painful: unable to swallow liquids; requires IV fluids
Clinical symptoms *not otherwise specified* in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values *not otherwise specified* in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism that study drug

10.6. Appendix 6: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0 – 2 yrs	NA	>150
QRS (msec)	0 - 2yrs	NA	>79
QT (msec)	0 - 2 years	NA	>500
RR (msec)	0 – 3 mo	<333	>750
	3 – 12 mo	<400	>860
	1 – 2 years	<430	>1000

Vital Signs

Normal ranges:

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

The following clinically relevant abnormalities will be defined for vital signs

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

References:

http://www.docstoc.com/docs/88983719/Pediatric-Vital-Signs
http://www.coheadquarters.com/PennLibr/MyPhysiology/Appendix/AppendVital1.htm

10.7. Appendix 7: 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 participants 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 participant 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 participants and site staff. If, at any time, a participant'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, participants' parents/caregivers will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants' 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 participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant's 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 participant has tested positive for COVID-19 during the study, (s)he should be withdrawn from the study. 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 participants' 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 CRF/eSource by the site personnel where needed.

- Administration of the study intervention:
  - If a participant 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 participant's home to:
    - Instruct participants' 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) [as per sponsor dosing instructions].
    - Administer the first study intervention themselves or supervise the participants' parent/caregiver during first study intervention administration.
    - Monitor any AEs related to dosing.
  - The date and time of the study intervention administration at the participant's home at Day 1 will be documented in the participant's source documents and in the CRF.
- Participant Visits/Assessments:
  - Upon an ARI alert, parents/caregivers need to take a nasal swab at home. If a study specific on-site visit cannot be conducted due to COVID-19 pandemic, a phone visit will be conducted by the site staff to assess the participant's health status remotely. If there is a medical need for the participant to have physical contact with a physician or for hospital based care, the parent(s)/caregiver(s) and participant will be invited to the site for a SOC visit and follow SOC procedures for hospital visit; therefore, no study related procedures will be performed, unless site staff and parent(s)/caregiver(s) can agree to perform (some of) the study assessments if allowed by local regulations during the COVID-19 pandemic. The parent(s)/caregiver(s) will continue answering the mobile App until a next alert. The optional stool samples will be collected in case the parent(s)/caregiver(s) has/have consented to this.
  - If a participant 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, Clinician PRESORS and clinical evaluation) for that particular visit is collected. These assessments and collection should be performed at participant's home by trained delegated site staff or home health service staff.
  - There are some assessments that could be conducted virtually via telephone (or videoconference, eg, Facetime, Skype, if possible) with participants' parent(s)/caregiver(s) in their homes. This methodology can only be used in accordance

with applicable (including local) laws, regulations, guidelines and procedures and with consent of participants' parent(s)/caregiver(s). These virtual assessments include review of AEs, concomitant medications and monitoring of parent(s)/caregiver(s) PRESORS completion. Please note, the visit windows included in the Schedule of Activities are still applicable. It must be documented in the CRF and in the participant's source documents if 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 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 not be 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.

10.8. Appendix 8: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	13-Jul-2020
Amendment 2	05-Jun-2020
Amendment 1	06-Nov-2019
Original Protocol	23-May-2019

11. REFERENCES

1. American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and Management of Bronchiolitis. Pediatrics. 2006;118:1774-1793.
2. Colman PM, Lawrence MC. The structural biology of type I viral membrane fusion. Nat. Rev. Mol. Cell Biol. 2003; 4(4):309-319.
3. Emergency Medicine Cases. Episode 59: Bronchiolitis. Available at: https://emergencymedicinecases.com/episode-59-bronchiolitis/. Accessed 19 March 2019.
4. Empey KM, Peebles Jr RS, Kolls JK. Pharmacologic Advances in the Treatment and Prevention of Respiratory Syncytial Virus. Clin Infect Dis. 2010; 50(9):1258–1267.
5. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Microbiol Rev. 2000;13(3):371-384.
6. Feltes TF, Sondheimer HM. Palivizumab and the prevention of respiratory syncytial virus illness in pediatric patients with congenital heart disease. Expert Opin. Biol. Ther. 2007; 7(9):1471-1480.
7. Garcia-Mauriño C, Moore-Clingenpeel M, Thomas J, Mertz S, Cohen DM, Ramilo O et al. Viral load dynamics and clinical disease severity in infants with respiratory syncytial virus infection. J Infect Dis. 2019;219(8):1207-1215.
8. Glezen W, Taber L, Frank A, et al. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986:140;543-546.
9. Hall C, Weinberg G, Iwane M, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360:588-598.
10. Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011 Jan 1;89(1):46-53.
11. https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. ICH 12 May 2005.
13. Investigator's Brochure: JNJ-53718678, Edition 06. Janssen Research & Development (July 2019).
14. Investigator's Brochure: JNJ-53718678, Addendum to Edition 06. Janssen Research & Development (April 2020).
15. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. Scand J Infect Dis. 2011;43:609-615.
16. Leidy N, Margolis M, Marcin J, et al. The impact of severe respiratory syncytial virus on the child, caregiver, and family during hospitalization and recovery. Pediatrics. 2005;115(6):1536-1546.
17. Leung AK, Kellner JD, Davies HD. Respiratory Syncytial Virus bronchiolitis. J Natl Med Assoc. 2005;97:1708-1713.
18. Lewis S, DeMuro C, Block SL, et al. Development of a novel observer-reported outcome measure for the assessment of Respiratory Syncytial Virus (RSV) infection symptoms in pediatric clinical trials. JPRO. 2018;2:9.
19. Nair H, Nokes JD, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010; 375(9725):1545-1555.
20. Piedra P, Stark A. Patient education: Bronchiolitis (and RSV) in infants and children (beyond the basics). Available at: https://www.uptodate.com/contents/bronchiolitis-and-rsv-in-infants-and-children-beyond-the-basics. Accessed 19 March 2019.
21. Ralston S, Lieberthal A, Meissner H, et al. Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics. 2014;134(5):e1474-e1502. Erratum in: Pediatrics. 2015;136(4):782.
22. Rivera CA, Gómez RS, Díaz RA, et al. Novel therapies and vaccines against the human respiratory syncytial virus. Expert Opin Investig Drugs. 2015;24:1613-1630.
23. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull. World Health Organ. 2008; 86(5):408-416.
24. Shi T, McAllister D, O'Brien K, et al. for the RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-958.
25. Wainwright C. Acute viral bronchiolitis in children – a very common condition with few therapeutic options. Paediatr Respir Rev. 2010; 11(1):39-45.

26. Yusuf S, Piedimonte G, Auais A, et al. The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. Epidemiol Infect. 2007;135:1077-109.
27. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. Clin Infect Dis. 2012;54:1427-1436.

INVESTIGATOR AGREEMENT

JNJ-53718678
Clinical Protocol 53718678RSV2006 Amendment 3

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): Mohamed Gamil, MD, M.Sc.

Institution: Janssen Research & Development

Signature: Mohamed Gamil Digitally signed by Mohamed Gamil DN: cn=Mohamed Gamil, o, ou, email=mgamil@its.jnj.com, c=BE Reason: I am approving this document Date: 2020.07.13 18:16:16 +02'00' 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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 148
Status: Approved, Date: 13 July 2020