Janssen Research & Development *

Clinical Protocol

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

Protocol 53718678RSV2004; Phase 2a
AMENDMENT 1

JNJ-53718678

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

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Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	26 Sep 2017
Amendment 1	24 April 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (24 April 2019)

The overall reason for the amendment: The overall reason for the amendment is to replace for all newly enrolled subjects after approval of this amendment the Respiratory Infection-Patient Reported Outcomes (RI-PRO) questionnaire by the Respiratory Infection Intensity and Impact Questionnaire (RiiQ) for the assessment of the duration and severity of signs and symptoms of respiratory syncytial virus (RSV) infection as reported by the subject.

Applicable Section(s)	Description of Change(s)

Rationale: The RI-PRO questionnaire was replaced by the RiiQ (which consists of the RiiQ Symptom Scale and the RiiQ Impact Scale), as RiiQ provides the patient's evaluation of both the severity of key symptoms of RSV disease (through the RiiQ Symptom Scale) and their impact on the patient's daily life (through the RiiQ Impact Scale), thereby providing a brief but more comprehensive assessment of the RSV disease and treatment experience than does a symptom severity rating scale (eg, RI-PRO). The RiiQ Symptom Scale measures the severity of 13 key symptoms of RSV disease so is suitable for twice daily patient diary by an acutely ill patient without overburdening the patient. The RI-PRO measures severity of 34 symptoms that may be associated with an influenza-like illness. However, many of the symptoms in the RI-PRO are not commonly experienced by adults with RSV disease, which makes RI-PRO unnecessarily long and potentially burdensome for RSV treatment studies. The less common symptoms of influenza-like illnesses in the RI-PRO can make scores difficult to interpret because they are often confounded with common comorbidities. It poses an unnecessary burden on acutely ill patients to report rare and less important symptoms in twice daily diaries. The short RiiQ Symptom Scale may avoid these limitations of the RI-PRO and provide insight into impact of RSV disease on the subject's health-related quality of life. As the RiiQ Symptom and Impact Scales can be assessed independently, it is possible to assess symptoms in the morning, and impact in the evening when the majority of impact issues are most relevant.
All newly enrolled subjects after approval of this amendment will need to complete the RI-PRO questionnaire, in addition to the RiiQ Symptom Scale, at Screening/Baseline and at Day 8 to allow for bridging between the RI-PRO data and the RiiQ Symptom Scale data to enable conclusions on the totality of the collected PRO data.

SYNOPSIS
ABBREVIATIONS
TIME AND EVENTS SCHEDULE
2.1.2 Endpoints
9.1.2 Screening Phase
9.2.2 Clinical Severity and Clinical Course of RSV Infection
11.4.2 Clinical Severity and Clinical Course of RSV Infection
Attachment 7

Rationale: Inclusion criterion #2 was updated to clarify that the legal age of consent in the jurisdiction in which the study is taking place is binding for eligibility, if this is >18 years

SYNOPSIS
4.1 Inclusion Criteria

Rationale: The Time and Events Schedule was updated to include the Medical Resource Utilization assessment to align with Section 9.6 (Medical Resource Utilization).

TIME AND EVENTS SCHEDULE

Applicable Section(s)	Description of Change(s)
	Rationale: The protocol was updated to indicate that laboratory abnormalities will be determined according to the criteria specified in the DMID adult toxicity tables (instead of the WHO Toxicity Grading Scale) to align with the toxicity tables included in Attachment 1.
9.7 Safety Evaluations 11.8 Safety Analyses	
	Rationale: The precision for the sample size calculation was updated without affecting the sample size itself. While correct information was considered for the sample size calculation, a precision estimate for the difference was considered to be more relevant. Precision (90% confidence interval [CI] half width) corresponding to the estimates for 1 group were included instead of the precision for the difference for 2 equally sized groups (active versus placebo).
SYNOPSIS 11.3 Sample Size Determination	
	Rationale: The protocol was updated to indicate that for some items data may be recorded directly into the eCRF and will be considered source data, instead of mandating such recording, to allow more flexibility as the source data may differ for each site.
17.4 Source Documentation	
	Rationale: The protocol was updated to remove inconsistencies between exclusion criterion #16 and Section 8 (CONCOMITANT THERAPY) regarding the administration of investigational vaccines and investigational drugs prior to the study.
4.2 Exclusion Criteria	
	Rationale: The TIME AND EVENTS SCHEDULE was updated to extend the time window of the first postdose ePRO assessment of the twice-daily schedule from 4 hours to 6 hours to help improve subject compliance with completion of the questionnaire.
TIME AND EVENTS SCHEDULE	
	Rationale: The protocol was updated to include Day 5 as additional timepoint for the assessment of the area under the RSV viral load-time curve (AUC), as AUC from immediately prior to first dose of study drug through Day 5 was also considered relevant to evaluate the antiviral effect.
SYNOPSIS 2.1.2 Endpoints 11.4.1 Antiviral Effect	
	Rationale: The TIME AND EVENTS SCHEDULE was updated to have the recording of the body temperature as a separate assessment to better reflect the actual timing of this assessment.
TIME AND EVENTS SCHEDULE	
	Rationale: The protocol was updated to provide additional clarification on the concomitant use of herbal supplements to align with the wording included in the Clinical Protocols of other clinical studies with JNJ-53718678.
8 CONCOMITANT THERAPY	
	Rationale: The protocol was updated to indicate that concomitant medication is not collected through the electronic device; these are captured in the eCRF only.
17.6 Patient-Reported Assessments	

Applicable Section(s)	Description of Change(s)
	Rationale: The protocol was updated to remove potential for drug-drug-interaction (DDI) as safety topic of special interest based on the evaluation of newly available nonclinical and clinical data. These data mainly indicate an increase in JNJ-53718678 exposure when coadministered with strong CYP3A4 inhibitors Given safety measures in place to ensure the subject's safety in this clinical study and because strong CYP3A4 inhibitors are not allowed as per Section 8 (CONCOMITANT THERAPY), the sponsor does not consider any longer potential for DDI a safety topic of special interest.
1.2.4 Potential Risks	
	Rationale: The protocol was updated to remove effects on blood coagulation as safety topic of special interest based on the evaluation of all available data, including most recent nonclinical and clinical data. Based on this evaluation, no signal with respect to blood coagulation is currently seen, and hence the sponsor does not consider any longer effects on blood coagulation a safety topic of special interest. However, samples for coagulation testing will continue to be collected as planned per TIME AND EVENTS SCHEDULE as a part of the standard safety monitoring in the study.
1.2.4 Potential Risks	
	Rationale: Minor errors were noted and corrected.
Throughout the protocol.	

SYNOPSIS

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

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

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

Secondary Objectives

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

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

Exploratory Objectives

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

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

- Impact of RSV and its treatment on health-related quality of life (HRQOL).

Endpoints

Primary Endpoint

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

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

Secondary Endpoints

The secondary endpoints are:

- Safety and tolerability, as assessed by adverse events (AEs), clinical laboratory testing, electrocardiograms (ECGs), vital signs, physical examination, throughout the study;
- Clinical course-related endpoints:
  - Duration and severity of signs and symptoms of RSV infection assessed through an instrument for patient-reported symptoms (either the Respiratory Infection-Patient Reported Outcomes [RI-PRO] questionnaire or the Respiratory Infection Intensity and Impact Questionnaire [RiiQ] questionnaire) and additional questions about health and functioning;
  - Time to resolution of selected RSV symptoms as reported by the subject (through either the RI-PRO or RiiQ);
  - Respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) as measured by the investigator;
- Pharmacokinetic parameters of JNJ-53718678, as determined by population pharmacokinetics (popPK) modelling.

Exploratory Endpoints

Exploratory endpoints include, but are not limited to:

- Antiviral activity and clinical course by stratification factor (time of symptom onset [≤3 days vs >3 days before randomization], severity of key RSV symptoms at screening), presence of comorbidities, baseline RSV viral subtype and genotype;
- The occurrence of complications with onset after treatment initiation that are associated with RSV per investigator assessment:
  - Bacterial superinfections (eg, pneumonia, sinusitis, bronchitis, bacteremia of presumed respiratory origin per investigator assessment);
  - Exacerbations of underlying pulmonary disease (eg, asthma, chronic obstructive pulmonary disease [COPD]);
  - Exacerbations of underlying cardiovascular conditions.
- The need for antibiotics related to complications associated with RSV per investigator assessment;

- Sequence changes (post baseline) in the RSV F-gene, and other regions of the RSV genome (at the request of the protocol virologist), as compared to baseline;
- Medical resource utilization;
- Association between clinical course of RSV and self-rated HRQOL.

Hypothesis

As this is an exploratory, hypothesis-generating study, no formal statistical hypothesis testing will be performed.

OVERVIEW OF STUDY DESIGN

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

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

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

Study participants will be identified when they present for medical care with symptoms supporting a diagnosis of RSV infection (eg, fever, cough, nasal congestion, runny nose, sore throat, myalgia, lethargy, shortness of breath, or wheezing). Screening should be completed as soon as possible; treatment initiation should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. During screening, mid-turbinate nasal swabs will be collected for local diagnosis of RSV infection (using a rapid polymerase chain reaction (PCR)-based or rapid-antigen-detection test), and for additional post-hoc analysis at a central laboratory to confirm RSV infection (and subtype), to determine RSV viral load and the presence of other viral or bacterial pathogens.

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

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

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

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

Subjects will be required to have a study visit at the study site or, if feasible, at home, on Day 3, Day 8, Day 14 (±1), and Day 21 (±3). On Day 28 (±3), subjects will be contacted by site staff for a telephone follow-up visit. In case subjects are experiencing ongoing AEs or have clinically significant laboratory abnormalities at time of the Day 21 follow-up visit, subjects might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site or, if feasible, at home on Day 28 (±3).

Study drugs will be administered orally. Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. The first dose of study drug will be administered before the subject leaves the site. On Day 1, study-site personnel can dispense to the subject all the required study drug for dosing at home, but partial dispensing at other visits is also allowed. Study-site personnel will instruct subjects on how to use and store study drug for at home dosing. Dosing should occur preferably at approximately the same time each day. Study drug can be administered without regard to meals and is preferably followed by drinking a glass of water.

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

Viral resistance will be monitored by sequencing of the viral F-gene on all baseline samples and on post baseline samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at the request of the protocol virologist. Sequencing data will not be reported to the investigators.

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

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model.

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

Medical resource utilization will be assessed.

Blood samples for host mRNA assessment may be used for exploratory biomarker analyses to determine the effects of JNJ-53718678 on markers of RSV disease at the sponsor's discretion. Leftover mid-turbinate nasal swabs and blood samples collected for other testing may be used as well for the same purpose.

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

A Data Review Committee (DRC) will be in place for this study. The DRC will monitor safety data during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring. The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the interim results and other ongoing studies of JNJ-53718678. These changes will be communicated in writing to investigators, health authorities, and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and will be implemented without amendment to this protocol.

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a Withdrawal and a Safety Follow-up Visit. Subjects who withdraw consent during

the treatment or follow-up phase will be offered and be encouraged to attend an optional Safety Follow-up Visit.

SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible after presentation to the healthcare facility, such that subjects are randomized (within a maximum of 5 days after RSV symptom onset) and treatment is initiated as soon as possible (but no later than 4 hours after randomization).

Key Inclusion Criteria

- Male or female, ≥18 years of age. If the legal age of consent in the jurisdiction in which the study is taking place is >18 years, this respective legal age is binding for eligibility.
- With an acute respiratory illness with signs and symptoms consistent with a viral infection (eg, fever, cough, nasal congestion, runny nose, sore throat, myalgia, lethargy, shortness of breath, or wheezing) with onset ≤5 days from the anticipated time of randomization. Onset of symptoms is defined as the time the subject becomes aware of the first sign and/or symptom consistent with a viral infection. Efforts should be made to determine the time of onset of symptoms as accurately as possible (in relation to routine daily activities). The viral infection may present in any way as long as the underlying precipitant of the illness is considered by the investigator to be due to RSV infection (examples: an upper or lower viral respiratory tract infection, pneumonia, respiratory distress, asthma exacerbation, COPD exacerbation).
- Diagnosed with RSV infection using a rapid PCR-based (preferably locally available) or rapid-antigen-detection test. (If a patient has a positive similar diagnostic test from another study and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility.)
- Medically stable (with the exception of the RSV-related illness) on the basis of physical examination, medical history, vital signs, and ECG performed at screening. If there are abnormalities, they must be consistent with the underlying condition (RSV disease and/or comorbid condition) in the study population as evaluated by the investigator (with exception of QTcF interval >500 ms, see exclusion criteria).
- A woman must be not of childbearing potential defined as premenarchal, postmenopausal, or permanently sterile.

Key Exclusion Criteria

- Hospitalized or expected to be hospitalized within 24 hours of screening. Any stay in the emergency room or in the observational unit of at least 24 hours will be considered hospitalization for the purposes of the study.
- Immunocompromised, in the opinion of the investigator, within the past 12 months, whether due to underlying medical condition (eg, malignancy or genetic disorder other than immunoglobulin A deficiency, or human immunodeficiency virus [HIV] infection) or medical therapy (eg, medications other than corticosteroids for the treatment of COPD or asthma exacerbations, chemotherapy, radiation, stem cell or solid organ transplant).
- Known or suspected chronic or acute hepatitis B or C infection.
- Unwilling to undergo mid-turbinate nasal swab procedures or any physical abnormality which limits the ability to collect regular nasal specimens.
- Confirmed QTcF interval >500 ms per the machine read parameter result at screening. Confirmation needs to be obtained by repeat triplicate ECG recording prior to dosing.

DOSAGE AND ADMINISTRATION

The subjects will receive the treatments as described in the table below. Study drugs will be administered orally.

Treatment	Dosing Regimen	Volume and Formulation
A	500 mg JNJ-53718678 once daily for 7 days	8 mL + 42 mL oral solution of JNJ-53718678[a]
B	80 mg JNJ-53718678 + matching placebo once daily for 7 days	8 mL oral solution of JNJ-53718678[a] + 42 mL of matching placebo solution
C	placebo once daily for 7 days	8 mL + 42 mL matching placebo solution

[a] JNJ-53718678 is formulated as an oral solution containing 10 mg/mL of active drug substance (G024). The matching placebo consists of the oral vehicle solution without active drug substance (G026).

Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. Study drug administration should occur once daily at approximately the same time each day. JNJ-53718678/placebo can be administered without regard to meals and is preferably followed by drinking a glass of water. Each dosing day, the same total volume of study drug solution should be administered, ie, 50 mL, divided over 2 separate but sequential intakes (1 container with 8 mL and 1 container with 42 mL).

EFFICACY EVALUATIONS

Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal secretions, obtained via mid-turbinate nasal swab, will be measured at the central lab using a qRT-PCR assay. Mid-turbinate swab specimens for the determination of the RSV viral load will be collected at several time points during the study.

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

If feasible, the RSV infectious virus titers as measured by quantitative culture of RSV (plaque assay) on selected nasal swab samples, may also be assessed.

Clinical Severity and Clinical Course of RSV Infection

The following evaluations of the clinical course of RSV infection will be performed throughout the study:

- Clinical parameters: respiratory rate, heart rate, SpO_2, and body temperature as measured during site visits. Subjects will be provided a thermometer and asked to record body temperature in the electronic device at home.
- Evolution and severity of signs and symptoms of RSV disease as assessed by the subject on a hand-held electronic device using the RI-PRO, the RiiQ Symptom Scale (if the subject was enrolled after approval of this amendment), and additional questions about health and functioning. Symptoms reported in the RiiQ Symptom Scale or RI-PRO will not be reported as AEs but constitute a part of the efficacy evaluations. Subjects will also complete the 5-level EuroQol 5-Dimension (EQ-5D-5L) and the RiiQ Impact Scale (for subjects who were enrolled after approval of this amendment) on the electronic device to rate their HRQOL.
- Need for hospitalization or medically attended visits (other than the study mandated visits) during treatment and follow-up.

Viral Sequencing

Viral resistance will be monitored by sequencing of the F-gene of the viral genome on all baseline samples and on post baseline samples upon request of the sponsor's protocol virologist. Other regions of

the RSV genome may also be sequenced at the request of the protocol virologist. Sequencing data will not be reported to the investigators.

PHARMACOKINETIC EVALUATIONS

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. Venous blood samples for determination of JNJ-53718678 plasma concentrations will be collected. Samples can also be used for the analysis of metabolites of JNJ-53718678, excipients (eg, hydroxypropyl-β-cyclodextrin), protein binding, or endogenous markers for enzymes or transporters involved in the metabolism or distribution of JNJ-53718678, at the discretion of the sponsor.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

The relationship between the pharmacokinetics and pharmacodynamics (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be evaluated.

BIOMARKER EVALUATIONS

Blood samples for host mRNA assessment may be used for exploratory biomarker analyses (eg, proteins including cytokines), on the premise that these markers may play a role in the treatment response, safety or pharmacokinetics of JNJ-53718678, or RSV-related disease. Leftover mid-turbinate nasal swabs and blood samples collected for other testing may be used as well for the same purpose. Analyses of biomarkers will be conducted at the sponsor's discretion and may be reported separately from this study.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data will be collected in the electronic case report form (eCRF) for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will include:

- Number and duration of medical care encounters: hospitalizations, physician or emergency room visits, test, and procedures, including surgeries, and other procedures (inpatient and outpatient) for RSV infection or complications associated with RSV per investigator assessment.

SAFETY EVALUATIONS

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

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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

- AEs, serious AEs (SAEs), and deaths;
- Clinical laboratory tests (blood and urine);
- ECG (12-lead);
- Vital signs (systolic and diastolic blood pressure):
- Physical examination (including height [only at screening] and body weight measurements) and skin examination.

OTHER EVALUATIONS

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

STATISTICAL METHODS

The primary (final) analysis will be performed after the last subject has completed his/her last visit of the study.

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

Investigators, subject(s) and local sponsor representatives will remain blinded. The central sponsor team members will be unblinded at the time of the interim analysis.

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

Sample Size

The interim results (estimates of mean AUC and change from baseline of the RSV viral load ±standard deviation [SD]) of study 53718678RSV1005 were the basis of the sample size calculation. In this study, median (range) time to onset of symptoms was 5 (2-12) days and baseline viral load was 5.3 (2.1-8.3) $\log_{10}$ copies/mL.

For the AUC viral load from Day 1 to Day 7, a (placebo) point estimate of 490 and an SD of 135 $\log_{10}$ copies x hr/mL was observed for the AUC viral load from Day 1 to Day 7. The sample size was determined in order to obtain estimates of the mean AUC viral load with a precision of approximately 50 $\log_{10}$ copies x hr/mL of the true value with 90% confidence; with 20 subjects per treatment group the half-width of the 90% confidence would be approximately 52 and with 24 subjects per treatment group the precision would be approximately 47 $\log_{10}$ copies x hr/mL.

For the change from baseline (on Day 2 or Day 3), (placebo) point estimates of -0.11 and -0.33 and SDs of 1.85 and 1.56 $\log_{10}$ copies/mL, respectively, were observed. The observed difference (active versus placebo) was -1 to -2 $\log_{10}$ copies/mL. With an assumed SD of 1.85 $\log_{10}$ copies/mL, 20 subjects per treatment group will lead to a precision (90% confidence interval [CI] half width) of 0.986 and 24 subjects per treatment group to a precision of 0.896 $\log_{10}$ copies/mL for the estimate of the difference in mean change from baseline of one dose group versus placebo.

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

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

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

Efficacy Analyses

The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized subjects who received at least one dose of study treatment and who have a central lab-confirmed RSV infection.

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

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

If feasible, the RSV infectious virus titers as measured by quantitative culture of RSV (plaque assay) on selected nasal swab samples, may also be assessed.

Endpoints will be analyzed graphically and descriptively as described in the Statistical Analysis Plan (SAP). For continuous variables descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For viral efficacy parameters also 90% CIs will be computed comparing active dose groups versus placebo. For categorical variables, frequency tables will be presented. Kaplan-Meier Curves will be produced to graphically describe the time to event data.

To explore the antiviral effect, $\log_{10}$ 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, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors over time. The differences in the AUCs for active versus placebo will be derived using appropriate contrasts deriving least squares mean differences, including the 90% 2-sided CIs. Details will be provided in the SAP.

Subject's severity of their RSV symptoms, functioning, and HRQOL as reported through the PRO questionnaires will be summarized descriptively.

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

Additional analyses will be performed to investigate other endpoints, including exploratory endpoints. Details on these analyses will be provided in the SAP.

Pharmacokinetic Analyses

Population pharmacokinetic analysis of concentration-time data of JNJ-53718678 will be performed using nonlinear mixed-effects modelling. An updated popPK model will be developed with the current adult data combined with those of selected Phase 1 studies to support a relevant structural model. Available subject characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. This updated model will be used for the final pharmacokinetic parameters estimation for each subject with available data. For each dose, descriptive statistics including

arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum of the final pharmacokinetic parameters (AUC, predose plasma concentration, and possibly the maximum observed concentration) will be provided. The pharmacokinetic analyses will be detailed in an analysis plan. Analyses of other analytes (eg, excipients, metabolites) may be performed at the discretion of the sponsor.

A snapshot date for pharmacokinetic samples to be analyzed for the planned interim analysis will be defined. Samples collected before this snapshot 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 interim analysis database lock.

Pharmacokinetic/pharmacodynamic Analyses

Relationships of JNJ-53718678 population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored.

Biomarker Analyses

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

Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group.

Safety Analyses

Safety data will be presented descriptively. No statistical testing of safety data is planned.

Data Review Committee

A DRC, comprised of senior sponsor personnel outside of the central sponsor team and not involved in study conduct, will be established. The DRC will monitor safety data during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring.

The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the interim results and other ongoing studies of JNJ-53718678. These changes will be communicated in writing to investigators, health authorities, and IECs/IRBs and will be implemented without amendment to this protocol.

TIME AND EVENTS SCHEDULE

Phase	Screening / Treatment		Treatment Phase				Follow-up[a]				
Day	**-1 to 1[b,c]**	**1**	**2**	**3**	**4-7**	**8**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**28 (±3)**
	Screening / Baseline On-site	**Treatment On-site**		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**		**On-site visit[d]**	**Phone follow-up (/ On-site visit)[d,e]**
Study Procedures											
Screening/Administrative											
Informed Consent	X										
Diagnostic ICF (optional)[c]	X										
Eligibility criteria[f]	X										
Subject characteristics and demographics	X										
Medical history/smoking habits/prior medications	X										
Blood sampling for HIV-1 and -2, hepatitis A, B & C serology	X										
Urine pregnancy test[g]	X									X	
Mid-turbinate nasal swab: RSV diagnosis (locally)[h]	X										
Mid-turbinate nasal swab: RSV diagnosis confirmation, RSV viral load, presence of other viral or bacterial pathogens (centrally)[i]	X										
Randomization		X[j]									
Study Drug Administration											
Dosing study medication[k]		X[l]	X	X	X						
Provision of study drug for daily use at home[m]		X									
Document dosing in study medication log		X	X	X	X						
Efficacy Assessments											
Clinical parameters[n]	X			X		X		X		X	X[o]

Phase	**Screening / Treatment**		**Treatment Phase**				**Follow-up**[a]				
Day	**-1 to 1**[b,c]	**1**	**2**	**3**	**4-7**	**8**	**9-13**	**14 (±1)**	**15-20**	**21 (±3)**	**28 (±3)**
	Screening / Baseline On-site	**Treatment On-site**		**On-site visit**[d]		**On-site visit**[d]		**On-site visit**[d]		**On-site visit**[d]	**Phone follow-up (/ On-site visit)**[d,e]
Body temperature[p]			X	X	X	X		X		X	X[o]
Mid-turbinate nasal swab: RSV viral load, viral sequencing[q,r]		X	X	X	X	X	X	X		X	
RI-PRO[s,]	X	X[u]				X					
RiiQ Symtom Scale[s]	X	bid[t]	bid	bid	bid	bid	bid	X	X	X	
Additional questions about health and functioning[s]	X	bid[t]	bid	bid	bid	bid	bid	X	X	X	
RiiQ Impact Scale[s,]	X	X[u]	pm	pm	pm	pm	pm	pm	pm	pm	
EQ-5D-5L[s]	X	X[u]	pm	pm	pm	pm	pm	pm	pm	pm	
Medical resource utilization	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments											
Vital signs[v]	X			X		X		X		X	X[o]
Physical examination[w]	X			X		X		X		X	X[o]
ECG (triplicate 12-lead)[x]	X			X[y]		X				X	X[o]
Clinical Laboratory Assessments											
Blood sampling for hematology and biochemistry[z,aa]	X					X				X	X[o]
Blood sampling for coagulation tests[aa]	X					X				X	
Urinalysis[aa,bb]	X					X				X	
Renal function testing[cc]	X					X				X	
Pharmacokinetics											
Blood sampling for pharmacokinetics of JNJ-53718678[dd]				X		X					
Exploratory Biomarker											
Blood sampling for host RNA assessment	X					X				X	

Phase	Screening / Treatment		Treatment Phase				Follow-up[a]				
Day	-1 to 1[b,c]	1	2	3	4-7	8	9-13	14 (±1)	15-20	21 (±3)	28 (±3)
	Screening / Baseline On-site	Treatment On-site		On-site visit[d]		On-site visit[d]		On-site visit[d]		On-site visit[d]	Phone follow-up (/ On-site visit)[d,e]
Continuous Subject Review											
Adverse events[ee]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[ff]	X	X	X	X	X	X	X	X	X	X	X

a. Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a Withdrawal and a Safety Follow-up Visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional 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.
b. Screening/baseline assessments start after signing of the ICF and can continue the next calendar day if needed. All screening/baseline procedures should take place prior to the first study drug intake.
c. Prior to signing the main consent form for the study, subjects may specifically allow for the collection and testing of nasal mid-turbinate swabs by signing the pre-screening (diagnostic) ICF.
d. If feasible, home visits are allowed instead of on-site visits.
e. Subjects will be contacted by site staff for a telephone follow-up visit. In case subjects are experiencing ongoing AEs or have clinically significant laboratory abnormalities at time of the Day 21 follow-up visit, subjects might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site or, if feasible, at home on Day 28 (±3).
f. Procedures performed as part of standard of care within approximately 48 hours prior to screening completion (ie, randomization) may be used in determining study eligibility. Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
g. For all female subjects a urine pregnancy test is to be performed on-site at screening and at selected time points.
h. If a patient has a positive similar diagnostic test from another study and meets all eligibility criteria for inclusion in this study, this diagnostic test result can be used for confirmation of eligibility.
i. One mid-turbinate nasal swab will be taken at screening and prior to administration of the first dose of study drug of which aliquots will be used for the central laboratory confirmation of RSV infection, to determine RSV viral load, to determine mutations in the viral genome potentially associated with resistance to JNJ-53718678, and to determine the presence of other viral or bacterial pathogens.
j. Subjects should be randomized within a maximum of 5 days after RSV symptom onset and treatment should subsequently be initiated as soon as possible, but no later than 4 hours after randomization. Randomization is to occur predose.
k. Study drugs will be administered orally once daily. Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. Dosing should occur once daily at approximately the same time each day. Study drug can be administered without regard to meals and is preferably followed by drinking a glass of water.
l. The first dose of study drug will be administered before the subject leaves the site.
m. On Day 1, study-site personnel can dispense to the subject all the required study drug for dosing at home, but partial dispensing at other visits is also allowed. Study-site personnel will instruct subjects on how to use and store study drug for at home dosing.
n. Clinical parameters include respiratory rate, heart rate, and peripheral capillary oxygen saturation (SpO_2) as measured during scheduled visits.

o. Assessment only to be performed if subject needs to have a follow-up visit on Day 28, per the investigator's judgement, for the follow-up of AEs or laboratory abnormalities on Day 21 (see also footnote e).
p. Subjects are to measure their body temperature at home on non-visit days using only a digital oral thermometer that will be provided on Day 1. This thermometer will also be used at baseline and during site visits. Subjects will be instructed how to use the thermometer, and to wait for the audible beep before recording their body temperature in the electronic device at home. Subjects will be instructed to bring the thermometer for use by the site staff during scheduled on-site visits. To be recorded in the temperature log on the electronic device when measured at home and in the eCRF during on-site visits.
q. Mid-turbinate nasal swabs will be taken to assess RSV viral load and emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678. The RSV infectious virus titers as measured by quantitative culture of RSV (plaque assay) may be assessed on selected nasal swab samples (pending feasibility of performing such an assay). Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). The first mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study drug (on Day 1). The next swabs (from Day 2 to Day 8) should be collected preferably at approximately the same time as on Day 1 each day. On Day 8, the investigator will check whether the subject is still symptomatic. For asymptomatic subjects swabbing will be stopped. For subjects still symptomatic, swabbing will be continued daily until the subject becomes asymptomatic or until Day 13 at the latest. Whether a subject is still symptomatic will be checked with daily telephone calls between the subject and site staff (and/or by review of the transmitted electronic patient-reported outcome [ePRO] data) in case swabbing is performed by the subject (or his/her spouse, partner, relative, or other caregiver) or by an HCP other than investigational site staff. On Day 14 and Day 21, a swab will be collected during the scheduled visit. During scheduled visits on Day 1, Day 3, Day 8, Day 14, and Day 21, swabs must be collected by a healthcare professional (HCP) (investigator/study-site personnel). On the other days, mid-turbinate swabs are collected at home preferably by an HCP and, only if not possible by an HCP, by the subject (or his/her spouse, partner, relative, or other caregiver) after being properly trained by the investigator/study-site personnel. In case preferred by the subject, all mid-turbinate swabbing may also be performed at the site. Date and time of swabs collected at home need to be recorded on the electronic device in a swabbing log. All subjects will be given appropriate mid-turbinate nasal swabs and Universal Transport Medium (same supplies as those used to collect nasal samples at the sites) to collect mid-turbinate nasal swabs. All swabs collected at home should be stored immediately between 2°C and 8°C (in the refrigerator) and brought to the site at the latest at the Day 3, Day 8, and Day 14 visit.
r. Leftover nasal samples may be used for exploratory biomarker research at the discretion of the sponsor.
s. . An electronic device will be provided to the subjects during screening and the investigator/study-site personnel will provide sufficient information to enable the subjects to complete these assessments.
t. The assessment of the RiiQ Symptom Scale and the additional questions about healthy and functioning should be completed once at screening, then twice daily (bid; in the morning and in the evening) from Day 1 to Day 14 and then once daily in the evening until the Day 21 visit. The first assessment of the twice-daily schedule on Day 1 needs to be completed as close as feasible and prior to the first administration of study drug. If screening and dosing are on the same day and the subject completed the screening assessment fewer than 3 hours prior to dosing, the predose assessment on Day 1 does not need to be performed. The first postdose assessment of the twice-daily schedule must be performed 12 hours ±6 hours after dosing (whether on Day 1 or on Day 2). The next assessment is performed at the subsequent time point (morning or evening) of the bid schedule, which will be followed through Day 14. Investigational staff will review regularly (preferably daily) the completion of the assessments of patient-reported symptoms and functioning and the logs once data is transmitted from the electronic device and contact the subject in case there are issues identified with completion of the assessments.
u. The assessment of the RI-PRO, the RiiQ Impact Scale, and the EQ-5D-5L on Day 1 needs to be completed as close as feasible and prior to the first administration of study drug. If screening and dosing are on the same day and the subject completed the screening assessment fewer than 3 hours prior to dosing, the predose PRO assessment on Day 1 does not need to be performed.
v. Vital signs include systolic and diastolic blood pressure (sitting or supine [same position at each measurement] after at least 5 minutes rest).
w. Physical examination includes height (only at screening), body weight measurements and skin examination.
x. Triplicate 12-lead ECGs will be obtained. ECGs may be repeated at the discretion of the investigator to rule out erroneous readings. ECGs will be obtained in a supine position after 5 minutes rest. If an ECG is scheduled at the same time point as other assessments, the ECG should be performed first.

y. ECG is to be performed post-dose (if feasible, 4 hours after dosing; otherwise as late as possible prior to leaving the site).
z. Biochemistry blood samples at Day 8 and Day 21 will be taken preferably under fasted conditions (fasted for at least 10 hours).
aa. Safety and coagulation laboratory tests will be done for each subject. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Any values that indicate a potential safety concern will be assessed by the investigator and appropriate follow-up actions, including potential discontinuation from treatment, will be carried out. Leftover blood samples may be used for exploratory biomarker analyses.
bb. Urinalysis will be performed by the central laboratory and includes dipstick analysis, and if needed microscopic examination.
cc. Includes determination of serum creatinine and estimation of the Glomerular Filtration Rate (GFR) based on creatinine by the Cockcroft-Gault formula[25]; determination of serum cystatine C and estimation of the GFR based on cystatine C[25]; determination of urinary creatinine, albumin, *N*-acetyl-β-glucosaminidase, β_2-microglobulin, urinary phosphorus, sodium, potassium, and calcium.
dd. Blood samples for determination of plasma concentrations of JNJ-53718678 will be collected on Days 3 and 8 at a random time point during the visit. The following information need to be recorded on the requisition form and/or the study medication log: date and time of study drug intake, date and time of pharmacokinetic blood sampling, time of meal if any in the time window of 2 hours before and 2 hours after study drug intake on the day of pharmacokinetic sampling. Samples can be used for the determination of plasma concentrations of metabolites of JNJ-53718678, excipients (eg, hydroxypropyl-β-cyclodextrin), protein binding, or endogenous markers for enzymes or transporters involved in the metabolism and distribution of JNJ-53718678, at the discretion of the sponsor.
ee. All AEs and SAEs will be collected continuously from signing of the ICF (including diagnostic ICF, if applicable) onwards until the last follow-up visit (end of study visit). Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
ff. Concomitant medication will be recorded by the site staff in the eCRF based on the electronic medication log records completed by the subject.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the RSV viral load-time curve
AUC_{xh}	area under the RSV viral load-time curve from 0 to *x* hours
AUC_{∞}	area under the RSV viral load-time curve from time 0 to infinity
bid	twice daily
C_{avg}	average plasma concentration at steady-state over the dosing interval
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COPD	chronic obstructive pulmonary disease
C_{trough}	predose plasma concentration
CYP	cytochrome P450
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
(e)GFR	(estimated) Glomerular Filtration Rate
(e)PRO	(electronic) patient-reported outcome(s)
EQ-5D-5L	5-level EuroQol 5-Dimension
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HCP	healthcare professional
HIV	human immunodeficiency virus
HP-β-CD	hydroxypropyl-β-cyclodextrin
HRQOL	health-related quality of life
IB	Investigator's Brochure
IC_{50}	50% inhibition concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IKr	cardiac inward potassium membrane current
IRB	Institutional Review Board
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MDE	multiple-dose escalation
MRU	medical resource utilization
NAP	not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PND	post-natal day
popPK	population pharmacokinetics
PQC	Product Quality Complaint
(e)PRO	(electronic) patient-reported outcome(s)

PT	prothrombin time
q24h	every 24 hours
qd	once daily
qRT-PCR	quantitative reverse transcription polymerase chain reaction
QTcF	QT-interval corrected for heart rate according to Fridericia
RBC	red blood cell
RI-PRO	Respiratory Infection-Patient Reported Outcomes
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire™
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time to reach C_{max}
TEAE	treatment-related adverse event
UGT	uridine diphosphate glucuronyl transferase
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

DEFINITIONS OF TERMS

Comorbid subjects	Subjects who have comorbid condition(s) for severe RSV disease
Comorbid conditions for severe RSV disease	Eg, asthma, chronic obstructive pulmonary disease, cardiovascular disease, other chronic diseases
Electronic device	A device for patient-reported outcomes and functioning assessments
Otherwise healthy subjects	Subjects who do not have comorbid condition(s) for severe RSV disease
RSV viral load	The number of RSV RNA copies, determined in nasal secretions (nasal swab samples). The unit is RSV RNA copies/mL.

1. INTRODUCTION

Respiratory syncytial virus (RSV) is considered the most important virus causing acute lower respiratory tract infection (LRTI) and is a major cause of hospital admissions and death in young children worldwide.[18,22] In addition, LRTI results in substantial illness and morbidity in the elderly and adults with underlying chronic illnesses, underlying disorders of cellular immunity, or suppressed immune systems in hospitalized and community-based patients.[4,10,11,12,18,19,27] Prospective surveillance from 1975-1995 in 2,960 subjects 18-60 years of age identified 211 RSV infections (7%) by culture. The infections were symptomatic in 84% of subjects, involved only the upper respiratory tract in 74%, and included lower respiratory tract symptoms in 26%. Thirty-eight percent of the patients missed work and they were ill for mean of 9.5 days.[13]

Despite the large medical and economic burden, treatment options for RSV-associated bronchiolitis and pneumonia are limited: prophylactic treatment with passive immunization with the humanized monoclonal antibody palivizumab in pediatric patients, treatment with ribavirin, and supportive treatment such as oxygenation and mechanical ventilation are available in hospitalized patients.[9,26] In an outpatient setting, standard of care is limited to symptomatic treatment of the flu-like manifestations of the disease. There is an unmet medical need for prophylactic (pre- and post-exposure) as well as therapeutic treatment in both children and adults.

Recent studies in pediatric and adult populations have demonstrated that RSV viral load and severity of disease symptoms are closely correlated, and that the window between the onset of clinical symptoms (day 1 and day 3 for influenza and RSV, respectively) and peak viral load (day 2 and day 6 for influenza and RSV, respectively) is considerably longer for RSV than for influenza.[1,4,7,8] This increases the likelihood that direct antivirals (small-molecules or biologicals) can be viable RSV treatments and achieve high and sustained antiviral responses and improve disease outcome. Aspired treatment effects include reduction of viral shedding, the prevention of acute LRTIs, reduced need for hospitalization, and in case of hospitalization, shortening of stay in the hospital or intensive care unit by decreasing the need for mechanical ventilation, and reduced incidence of mortality.

Enveloped viruses like RSV have a complex membrane fusion machinery that includes a fusion protein that enables the deposition of the viral nucleic acid genome into the host cells and initiates their replication.[3,16] JNJ-53718678 is an investigational RSV specific fusion inhibitor belonging to the indole chemical class and is under development for the treatment of RSV infection. The study drug shows in vitro activity against a panel of viruses belonging to both the RSV subfamilies A or B. In addition, antiviral activity of JNJ-53718678 was demonstrated during clinical studies in healthy adults inoculated with RSV (study 53718678RSV2001) and in pediatric subjects hospitalized due to RSV-infection (study 53718678RSV1005).

For the most comprehensive nonclinical and clinical information regarding JNJ-53718678, refer to the latest version of the Investigator's Brochure (IB) for JNJ-53718678.[15]

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

1.1. Background

Nonclinical Studies

Nonclinical Profile

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.

Once daily 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 as well as lavaged-lung tissue as compared to animals that received vehicle only. Estimated EC_{50} for the average plasma concentration at steady-state was 753 ng/mL and 296 ng/mL for bronchoalveolar lavage fluid 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 gamma-induced protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein-1α, and interferon-1) was observed. Furthermore, RSV-induced gross lung lesion formation and concomitantly significant improvement of the general lung condition was observed (eg, reduction of bronchiolitis and lung neutrophilia). Together, these results demonstrate the efficacy of the study drug to inhibit RSV-induced lung pathology sequelae. No adverse signs or reactions in the animals that were dosed up to 25 mg/kg JNJ-53718678 were observed.[21]

In high-throughput screening ion channel voltage clamp assays, JNJ-53718678 did not affect cardiac inward sodium membrane current up to 10 μM, but slightly to markedly inhibited cardiac inward potassium membrane current (IKr) at concentrations starting at 1 μM. In a Good Laboratory Practice (GLP) human-ether-à-go-go-related gene study, the IKr blocking was confirmed with a 50% inhibition concentration (IC_{50}) of 1.9 μM. When JNJ-53718678 was given intravenously 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 single-dose 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 once daily in conscious dogs, heart rates were increased at all doses in most dogs and blood pressure was decreased at all dose levels 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 increased to 31,000 ng/mL after 5-day repeated dosing of JNJ-53718678 250 mg/kg once daily.

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

Pharmacokinetics and Metabolism in Animals

Following single intravenous administration to different preclinical species, JNJ-53718678 was cleared with a low to moderate clearance in male mice, dogs, and monkeys (equivalent to 11%-30% of liver blood flow) and a high clearance in male rats (93% of liver blood flow). The volume of distribution at steady-state was moderate in all species (1-3 L/kg), indicative of moderate distribution to tissues.

Rapid absorption from the gastrointestinal tract was observed across preclinical species after single oral JNJ-53718678 doses formulated in hydroxypropyl-β-cyclodextrin (HP-β-CD). Absolute bioavailability of JNJ-53718678 at 10 mg/kg (mice, rats) and 5 mg/kg (dogs, monkeys) was around 58% in mice, 42% in rats, 90% in dogs, and 21% in monkeys. 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 below 5-10 mg/kg. Feeding status had minimal to no impact on oral bioavailability of solution and suspension formulations at 5 mg/kg in dogs.

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 in vitro. Based on the observed rapid but passive uptake of JNJ-53718678 by suspended human hepatocytes, in vivo clearance of JNJ-53718678 will not likely be hepatic uptake-limited or sensitive to interactions with hepatic uptake inhibitors. In vitro, JNJ-53748678 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. JNJ-53748678 is not a substrate for OATP1A2 and OATP2B1 up to 15 μM. For multidrug and toxin extrusion protein 1 (MATE1) the IC_{50} was >8.5 μM and for MATE2-K the IC_{50} was ~8.5 μM.

Plasma protein binding of JNJ-53718678 was high in adult preclinical species (88% to 99%) and in adult humans (96%), and in juvenile preclinical species (92-93%). JNJ-53718678 preferentially binds to alfa-1-acid glycoprotein. Major metabolic pathways for JNJ-53718678 have been identified in human hepatocytes; these were oxidation, *N*-dealkylation, cleavage in the middle part of the molecule, and glucuronidation of oxidative metabolites. There was also evidence of direct *N*-glucuronidation, which was not observed in hepatocytes of rats and dogs. Cytochrome P450 (CYP) A4 is the major CYP enzyme involved in JNJ-53718678 phase 1 metabolism in human hepatocytes. Uridine diphosphate glucuronyl transferase (UGT) A3 and UGT1A4 are involved in direct *N*-glucuronidation.

There was no evidence for the formation of reactive intermediates.

In human hepatocytes, 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.

After giving repeated JNJ-53718678 doses to rats and dogs, JNJ-53718678 plasma exposure decreased dose-dependently in rats, indicating clearance via auto-induction, and increased dose-dependently in dogs.

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, gamma-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 and thrombocytes 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_{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. Adverse effects at the high dose (500 mg/kg/day) were related to coagulation.

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 [ALT] 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 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 as animals showed continuous body weight loss as a result of decreased food consumption, which was likely related to the ulceration/necrosis of the nonglandular 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 canaliculi 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_{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 observed and body weight loss in relation with decreased food consumption 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 stomach, the intestinal tract, and the hepatobiliary system.

Oral administration of JNJ-53718678 in adult 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_{24h} values were 4,710 ng/mL and 87,200 ng.h/mL, respectively. In minipigs dosed for 28 days at 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/day showed exposures overlapping with those observed in animals of the 35/50 mg/kg/day dose group, leading to adverse effects (decreased WBC count and RBC mass). Target organ systems in 25 and 35/50 mg/kg/day dose groups were primarily circulating white and RBCs, leading to hemosiderin deposition in the liver and adaptive changes in hematopoietic organs (bone marrow, spleen). The effects on white and RBCs in animals dosed at 35/50 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 2,120 ng.h/mL, and for female minipigs of 1,750 ng/mL and 3,150 ng.h/mL, respectively.

In the first pilot juvenile study in rats, in which pups 1 day of age (post-natal day [PND] 1) or 8 days of age (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 seen, as well as periodically slightly lower body weight gain associated with lowered food consumption 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_{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_{24h} 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 seen.

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 maximum tolerated dose, as the animal was sacrificed, after showing a poor clinical condition after 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 bone marrow (from 10 mg/kg/day onwards), lower bone marrow 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 with reticulocyte response and

increased (extramedullary) hematopoiesis, increased bilirubin levels, decreased fibrinogen levels, and body weight loss upon weaning. These findings were (mostly) reversible at the end of the 4-week recovery period. Minor to slight, non-adverse histopathologic findings were noted at 10 mg/kg/day. The NOAEL in this study was set at 10 mg/kg/day. Corresponding C_{max} and AUC_{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.

The use of HP-β-CD as excipient in the formulation of JNJ-53718678 in clinical studies in the adult and pediatric populations is supported by a range of (juvenile) toxicity studies. A dedicated GLP juvenile toxicity study in the rat revealed no new target organs or toxicities vs known toxicities from studies in adult animals. HP-β-CD is known to increase soft feces due to osmotic water retention in the large intestine. Other findings (eg, swelling and microvacuolation of renal cortical tubular cells, urothelium cells, increases in several urinary parameters) seen in (juvenile) animals were related to the renal excretion of HP-β-CD and were regarded as non-adverse, transient, adaptive responses.

The results of the safety pharmacology studies, genetic toxicology studies, and general toxicity studies in adult and juvenile rats, dogs, and minipigs support the administration of JNJ-53718678 to adult and pediatric human subjects. In healthy adult volunteers, JNJ-53718678 was well tolerated up to the highest dose tested, ie, 500 mg given once daily for 8 days, corresponding to mean exposure parameters of 2,660 ng/mL for C_{max} and 31,200 ng.h/mL for AUC on Day 8. In pediatric patients, exposure is not anticipated to exceed the exposure achieved in healthy volunteers at 500 mg once daily. At this dose, animal/human exposure safety ratios based on NOAELs in the GLP studies in juvenile rats and minipigs and data in healthy adult volunteers, were 5-11 for juvenile rats and 2 for juvenile minipigs.

Clinical Studies

Pharmacokinetics and Product Metabolism

Single Dose

In the single-dose escalation part of study 53718678RSV1001, 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 0 to infinity (AUC_{∞}) 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 hours. Mean terminal elimination half-life ranged from 9.3 to 10.3 hours for the 75-mg dose group to the 1,000-mg dose group and was somewhat lower for the 25-mg dose group with a value of 6.6 hours.

Based upon data from study 53718678RSV1004 in healthy Japanese adult men and study 53718678RSV1001, C_{max} and AUC_{∞} for JNJ-53718678 are similar between Caucasian and Japanese subjects after single dose administration.

Multiple Dose

In the multiple-dose escalation (MDE) part of study 53718678RSV1001 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_{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 q24h regimen. The total amount of JNJ-53718678 excreted in urine over the dosing interval at steady-state was low, 3.74%, 1.89% and 1.76% of the administered dose for, respectively, 250 mg q24h, 500 mg q24h and 250 mg twice daily. Renal clearance was very low, and similar between dose regimens.

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

Food Interaction

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_{∞} of JNJ-53718678 was 7% lower when JNJ-53718678 was administered under fed conditions compared with fasted conditions. Therefore, JNJ-53718678 can be taken with or without food.

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 likely 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 is 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). The results confirmed that CYP3A4 significantly contributes to the elimination of JNJ-53718678, as an approximately 3-fold increase in the total exposure of

JNJ-53718678 upon coadministration with itraconazole 200 mg once daily was observed. 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 once daily decreased the exposure of JNJ-53718678, primarily due to induction of CYP3A4. JNJ-53718678 C_{max}, AUC_{last}, and AUC_{∞} decreased to 19%, 8%, and 8%, respectively, of the reference value (administration of JNJ-53718678 alone).

Efficacy

In study 53718678RSV2001 in healthy adult subjects inoculated with RSV-A Memphis 37b virus, mean and median RSV viral load AUC from baseline until discharge were lower for all JNJ-53718678 dosing groups (75 mg once daily, 200 mg once daily, or 500 mg once daily 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, clinical proof-of-concept for JNJ-53718678 has been established.

In study 53718678RSV1005 in pediatric subjects hospitalized due to RSV infection, a clear trend towards an (early) antiviral effect of JNJ-53718678 is observed. An effect on viral load change from baseline on Days 2 and 3, 1 to 2 logs difference compared to placebo, was observed as well as an effect on viral load AUC on Days 3 and 7 (20 to 25% reduction compared to placebo). The observed trends are similar across JNJ-53718678 dose groups (1 mg/kg, 1.5 mg/kg, 2 mg/kg, or 6 mg/kg once daily).

Safety and Tolerability

Adult Population

During clinical studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, and 53718678RSV2001, a total of 184 adult subjects were enrolled of whom 150 received at least 1 dose of JNJ-53718678 as single doses up to 1,000 mg or multiple doses up to a total daily dose of 500 mg (as 500 mg once daily or 250 mg twice daily) for up to 13 days. Of those, 100 were healthy adult subjects and 50 were healthy adult subjects who were inoculated with RSV-A Memphis 37b virus.

During these studies, no deaths or other serious adverse events (SAEs) were reported. Four subjects discontinued study treatment due to an adverse event (AE):

- 1 subject from study 53718678RSV1001 discontinued study treatment due to an AE of grade 2 gastroenteritis, which started 52 days after having received a single dose of 75 mg JNJ-53718678 and was considered by the investigator to be doubtfully related to study treatment;

- 1 subject from study 53718678RSV2001 who received placebo discontinued study treatment due to an AE grade 2 urticaria, which was considered by the investigator to be possibly related to RSV-infection or study treatment;
- 1 subject from study 53718678RSV2001 from the 75 mg JNJ-53718678 group was reported with a grade 1 AE of electrocardiogram (ECG) QRS complex prolonged (verbatim: Prolonged QRS) on the first day of dosing. The ECG findings included a QRS complex width at baseline of 117 ms and prolongation to 120 ms at time of the start of the AE (QRS width normal range as per protocol: >50 ms to <120 ms). This AE was considered by the investigator to be possibly related to RSV infection or study treatment. Duration of the AE of ECG QRS complex prolonged was reported as 3 days, after which a grade 2 AE of ECG change (verbatim: change in morphology [from incomplete right bundle branch block]) was reported. This grade 2 AE led to withdrawal of the study medication and was considered by the investigator to be doubtfully related to RSV infection and possibly related to study treatment. At the last follow-up visit, 21 days after the onset of the grade 2 AE, this AE was considered resolved. The ECG reported an abnormally high QRS width with values fluctuating between 120 ms at start of the first AE and 138 ms at the end of the second AE;
- 1 subject from study 53718678RSV2001 from the 200-mg JNJ-53718678 group was reported with a grade 1 AE of ECG change (verbatim: nonspecific ECG change) on the third day of dosing, for which the study medication was withdrawn. The ECG was considered clinically significantly abnormal. This AE was considered by the investigator to be possibly related to RSV infection or study treatment. The AE was considered resolved 23 days after its onset.

For the purpose of reviewing the available clinical safety data, tables were created combining the results on AEs, laboratory abnormalities, abnormalities in vital sign parameters, and ECG abnormalities from studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001. It should be noted that in study 53718678RSV2001 the Division of Microbiology and Infectious Diseases (DMID) toxicity grading scale was used while the World Health Organization (WHO) toxicity grade scale was applied in the other studies. However, as the differences between these 2 grading scales are minimal, this did not affect the conclusions from this safety data review.

Furthermore, given that there was an unequal allocation of subjects to JNJ-53718678 and placebo in most studies and that in study 53718678RSV1002 no placebo group was included, the overall number of placebo subjects is low. Hence, this limits the ability to draw firm conclusions on the comparisons made in this section. In addition, most individual AEs and abnormalities were observed at low frequency, which further limits the comparison between JNJ-53718678 and placebo.

During clinical studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001, among subjects who received at least 1 dose of JNJ-53718678, 70% experienced an AE as compared to 46.7% of all subjects who received placebo. All but 1 of the treatment-emergent AEs (TEAEs) reported during these studies were either grade 1 or grade 2 in severity; 1 subject who received placebo was reported with a grade 3 headache in study 53718678RSV1001. Adverse events observed more frequently (difference in incidence of ≥5%) in subjects who had received at least 1 dose of JNJ-53718678 compared to subjects who received

placebo included diarrhea (20.8% vs 11.1%), dysgeusia (10.8% vs 0.0%), epistaxis (7.5% vs 0.0%), fatigue (6.7% vs 0.0%), abdominal discomfort (5.0% vs 0.0%), and hot flush (5.0% vs 0.0%).

In study 53718678RSV1006, 35.7% and 31.3% of the subjects from Panel 1 and Panel 2, respectively, experienced at least one AE. In this study, all reported AEs were grade 1, and except for abdominal discomfort (reported in 2 subjects [14.3%] in Panel 1), all AEs were reported in at most 1 subject.

In study 53718678RSV1001, dysgeusia was frequently reported in subjects receiving JNJ-53718678 and in none of the subjects of the placebo group. Dysgeusia was a frequently reported AE in subjects receiving JNJ-53718678 due to the bitter taste of the oral JNJ-53718678 formulation. This observation led to the initiation of study 53718678RSV1003 to select an optimized taste of the formulation for future studies.

In study 53718678RSV1002, diarrhea was reported by the vast majority of subjects. In addition, for 2 subjects the AE of "frequent bowel movements" was reported. Of note, no HP-β-CD-containing placebo solution was administered in this study. The incidence of the AE of diarrhea was similar in subjects receiving JNJ-53718678 and those receiving placebo in study 53718678RSV2001. The observed AEs of diarrhea in both these studies may be explained by the presence of 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. Furthermore, the AE of diarrhea was not reported in subjects receiving JNJ-53718678 in studies 53718678RSV1004 and 53718678RSV1001, where HP-β-CD was used as an excipient in the JNJ-53718678 and placebo oral formulations, while there was 1 subject reported with the AE of "frequent bowel movements" in study 53718678RSV1001. In study 53718678RSV1006 (no placebo administered), no cases of diarrhea or "frequent bowel movements" were reported. Hence, the observed imbalance in overall incidence of the AE of diarrhea is most likely the result of bias due to the absence of a placebo group in study 53718678RSV1002. Other gastrointestinal tract-related AEs were rare and generally more frequently reported in subjects receiving JNJ-53718678. However, due to their low incidence, no valid comparison could be made with subjects receiving placebo.

Epistaxis as a TEAE was only reported in study 53718678RSV2001, all events were grade 1 in severity, all were considered by the investigator to be not related to the study drug but at least possibly related to RSV, and were reported as recovered prior to the end of the study. The related verbatims included blood stained tissue from nasal mucosa, blood stained nasal wash, blood stained tissue from nasal bleeding, nasal bleeding right/left nostril, and blood spotting nasal wash. Of the 9 subjects who were reported with treatment-emergent epistaxis, 4 were also reported with this AE during the post-challenge phase, 2 during both the pre- and the post-challenge phase, 2 during the treatment phase only, and 1 during both the treatment and the follow-up phase. No association was observed between any of the events and changes in coagulation parameters. While epistaxis as TEAE was not reported in the subjects who received placebo, the observed incidence is consistent with the incidences observed in other RSV challenge studies.[5,6]

The AE of hot flush was only reported in the MDE part of study 53718678RSV1001 and no dose-related incidence was observed.

In general, none of the reported AEs occurred consistently across different studies and most occurred at a low incidence and low severity. Observed differences in incidence between subjects receiving JNJ-53718678 and those from the placebo group were small for most AEs, considering the limitations of the comparison in view of the difference in sample size of the JNJ-53718678 group and the placebo group. Based upon these AE data, no safety signal was identified for JNJ-53718678.

During clinical studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001, the incidences of graded and non-graded laboratory abnormalities were generally low in these studies. All graded laboratory abnormalities were either grade 1 or grade 2. Graded and non-graded laboratory abnormalities observed more frequently in subjects who had received at least 1 dose of JNJ-53718678 compared to subjects who received only placebo (difference in incidence of ≥5%) included prothrombin activity above normal (non-graded; 72.2% vs 39.1%), triacylglycerol lipase above normal (non-graded; 19.4% vs 13.0%), increased cholesterol (graded: 15.0% vs 8.9%), and eosinophil/leukocyte ratio below normal (non-graded; 7.5% vs 2.2%). Of note, the incidences of the graded laboratory abnormality of increased PT and aPTT were similar between subjects receiving JNJ-53718678 and those receiving placebo (15.8% vs 17.8% and 8.3% vs 11.1%, respectively). Changes in liver enzymes were observed in few subjects receiving JNJ-53718678 and in subjects receiving placebo, with similar incidences. Most of the observed laboratory abnormalities did not demonstrate a distinct difference in incidence between subjects receiving JNJ-53718678 and those receiving placebo.

In study 53718678RSV1006, results regarding graded and non-graded laboratory abnormalities were generally consistent with those of other studies.

None of the observed (non-)graded laboratory abnormalities was indicative of a safety signal for JNJ-53718678.

Changes in heart rate, blood pressure, or respiratory rate were observed in some subjects and were considered generally clinically insignificant during clinical studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001. These were either grade 1 or grade 2 in severity, except for 1 subject from study 53718678RSV1001 who received 1,000 mg JNJ-53718678 and in whom a grade 3 increase in respiratory rate was reported. Considering all of the safety data from clinical studies, a consistently greater incidence of any of the observed abnormalities in vital signs parameters was not apparent in subjects receiving JNJ-53718678 compared to subjects receiving placebo.

In study 53718678RSV1006, results on vital signs abnormalities were generally consistent with those of other studies.

During clinical studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, and 53718678RSV2001, no prolongations of the QT-interval corrected for heart rate according to

Fridericia (QTcF) were reported. Changes in ECG parameters were rare and considered clinically insignificant. Four ECG abnormalities were reported as AE in 3 subjects (2 subjects receiving JNJ-53718678, 1 subject receiving placebo), all during study 53718678RSV2001.

In study 53718678RSV1006, ECG abnormalities were scarce and results were generally consistent with those from other studies.

None of the observed abnormalities in vital signs parameters or ECG abnormalities suggested a safety signal for JNJ-53718678.

No clinically relevant physical examination findings were observed during these clinical studies.

In general, no relation was noted between the incidence of AEs, laboratory abnormalities, abnormalities in vital signs parameters, ECG abnormalities, or physical examination findings and the dose level and/or the dose regimen of JNJ-53718678.

In conclusion, during these clinical studies in healthy adults or adult subjects inoculated with RSV, JNJ-53718678 at single doses up to 1,000 mg and at multiple doses up to 500 mg once daily and 250 mg twice daily, were generally safe and well tolerated. These studies did not identify any safety signal for JNJ-53718678.

Pediatric Population

During the ongoing study 53718678RSV1005, 44 pediatric subjects hospitalized due to RSV infection were enrolled up to the cut-off date of 6 June 2017, of whom 37 subjects received JNJ-53718678 and 7 received placebo.

Interim results from study 53718678RSV1005 show that treatment with JNJ-53718678 is generally safe and well tolerated and no safety signals arose in pediatric subjects compared to the previously established safety profile in adults.

No grade 4 AEs or AEs leading to discontinuation were reported. Two grade 3 (severe) AEs of bronchiolitis (1 each in the JNJ-53718678 and placebo group, both serious) were reported. Four SAEs were reported, 2 in the JNJ-53718678 treatment group: rhinitis and bronchiolitis and 2 in the placebo group: pneumonia and bronchiolitis. These were considered not related to the study drug by investigator. Adverse events $\geq$ grade 2 and considered at least possibly related by the investigator were grade 2 (moderate) anemia (n = 1) and grade 2 leukocytosis (n = 1), both in the JNJ-53718678 treatment group.

Treatment-emergent laboratory abnormalities were infrequently reported and of low severity (maximal grade 2) but reported at somewhat higher incidences in the JNJ-53718678 treatment group.

No relevant differences were observed for vital signs abnormalities between JNJ-53718678 and placebo and no AEs related to vital signs abnormalities were reported.

No dose relationship was observed for the AEs, laboratory abnormalities or vital signs abnormalities.

1.2. Benefit-risk Evaluations

1.2.1. Known Benefits

JNJ-53718678 at daily doses of 75, 200, and 500 mg given for 7 days has shown an antiviral effect and reduced the signs and symptoms of RSV infection in healthy adults in an RSV human challenge model. In addition, JNJ-53718678 established proof of concept (antiviral effect) in the pediatric population based on interim data from study 53718678RSV1005 (Section 1.1). However, the clinical benefit of this compound remains to be established.

1.2.2. Potential Benefits

Subjects participating in this study might have a benefit regarding the clinical course of their RSV infection. Results from the proposed study may be useful in developing a new antiviral therapy for RSV infection.

1.2.3. Known Risks

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

1.2.4. Potential Risks

All therapies have the potential to cause adverse experiences.

During studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, and 53718678RSV2001, a total of 184 adult subjects were enrolled of whom 150 received at least 1 dose of JNJ-53718678 as single doses up to 1,000 mg or multiple doses up to a total daily dose of 500 mg (as 500 mg once daily or 250 mg bid) for up to 13 days. Of those, 100 were healthy adult subjects and 50 were healthy adult subjects who were inoculated with RSV-A Memphis 37b virus. In study 53718678RSV1003, 12 subjects were enrolled but they were only to taste and not to swallow the oral solutions of JNJ-53718678.

During the ongoing study 53718678RSV1005, 44 pediatric subjects hospitalized due to RSV infection were enrolled up to the cut-off date of 6 June 2017, of whom 37 subjects received JNJ-53718678 and 7 received placebo.

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

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

Based upon the limited available clinical data, no risk related to the hepatobiliary system was identified. However, given the hepatobiliary-related nonclinical findings and because the amount of clinical data is limited, the sponsor considers hepatobiliary effects to be a safety topic of special interest and hepatobiliary function will be monitored by routine hepatobiliary function tests.

Based upon the available clinical data, no risk related to the gastrointestinal tract was identified. However, given the nonclinical findings and because the amount of clinical data is limited, any clinical signs and symptoms related to the gastrointestinal tract will be monitored during clinical studies and appropriate clinical management will be installed.

In adult clinical studies with JNJ-53718678, renal-related laboratory abnormalities and AEs were only sporadically reported without a distinct difference in incidence between subjects receiving JNJ-53718678 and those receiving placebo. As the renal excretion of JNJ-53718678 is very limited, the potential for renal adverse effects is considered to be minimal. Based upon these data, no renal-related risks are anticipated. However, renal function will be monitored by renal function tests.

The evaluation of JNJ-53718678 antiviral activity requires nasal swabbing. However, this is a minimally invasive assessment that at most results in some short-term discomfort for the subject and is usually well tolerated, though occasionally nose bleeding can occur. The risks associated with blood sampling for safety or pharmacokinetic purposes are limited and the volume of blood needed is well below the acceptable limits for adults.

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

1.2.5. Overall Benefits/Risks

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

- Proof of concept was established in adult healthy volunteers challenged with a laboratory strain of RSV (study 53718678RSV2001) as well as in naturally RSV infected pediatric subjects (study 53718678RSV1005 [interim data]) (Section 1.1);
- The completed studies to date identified no safety concerns and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to JNJ-53718678 by the investigator (Section 1.1);
- Available interim data from the ongoing 53718678RSV1005 study in naturally RSV-infected pediatric subjects >1 month to ≤24 months of age did not indicate safety concerns (Section 1.1);
- Several safety measures have been proposed to minimize potential risk to subjects, including:

- Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study;
- Safety data on the highest dose selected for the current study did not identify any safety concern;
- Utilization of discontinuation and stopping criteria (see Section 10.2);
- Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development and safety topics of special interest of JNJ-53718678;
- The establishment of a Data Review Committee (DRC) to monitor data on a regular basis to ensure continuing safety of the subjects enrolled in this study.

1.3. Overall Rationale for the Study

This study will be performed to explore the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics of JNJ-53718678 in adult subjects infected with RSV. The results of this study will be used for selection of the dose and endpoints in subsequent studies.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

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

Secondary Objectives

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

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

Exploratory Objectives

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

- The relationship between antiviral activity and clinical course;

- The relationship between pharmacokinetics and pharmacodynamics (selected antiviral activity parameters, clinical outcomes, and safety parameters);
- Potential differences in antiviral activity and clinical course based on baseline characteristics, including but not limited to:
  - otherwise healthy and comorbid subjects;
  - subjects with symptom onset ≤3 days before randomization and subjects with symptom onset >3 days before randomization.
- The occurrence of complications associated with RSV per investigator assessment after initiation of treatment;
- Medical resource utilization (MRU), including hospitalization, for clinical management of subjects during treatment and posttreatment follow-up;
- The impact of the baseline RSV viral subtype and genotype on the antiviral activity and clinical course;
- The emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678;
- The RSV infectious virus titers as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay);
- Impact of RSV and its treatment on health-related quality of life (HRQOL).

2.1.2. Endpoints

Primary Endpoint

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

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

Secondary Endpoints

The secondary endpoints are:

- Safety and tolerability, as assessed by AEs, clinical laboratory testing, ECGs, vital signs, physical examination, throughout the study;
- Clinical course-related endpoints:

  - Duration and severity of signs and symptoms of RSV infection assessed through an instrument for patient-reported symptoms (either the Respiratory Infection-Patient Reported Outcomes [RI-PRO] questionnaire or the Respiratory Infection Intensity and Impact Questionnaire [RiiQ] questionnaire) and additional questions about health and functioning;
  - Time to resolution of selected RSV symptoms as reported by the subject (through either the RI-PRO or the RiiQ);
  - Respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) as measured by the investigator;
- Pharmacokinetic parameters of JNJ-53718678, as determined by population pharmacokinetics (popPK) modelling.

Exploratory Endpoints

Exploratory endpoints include, but are not limited to:

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

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

As this is an exploratory, hypothesis-generating study, no formal statistical hypothesis testing will be performed.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

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

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

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

Study participants will be identified when they present for medical care with symptoms supporting a diagnosis of RSV infection (eg, fever, cough, nasal congestion, runny nose, sore throat, myalgia, lethargy, shortness of breath, or wheezing). Screening should be completed as soon as possible; treatment initiation should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. During screening, mid-turbinate nasal swabs will be collected for local diagnosis of RSV infection (using a rapid polymerase chain reaction (PCR)-based or rapid-antigen-detection test), and for additional post-hoc analysis at a central laboratory to confirm RSV infection (and subtype), to determine the RSV viral load and the presence of other viral or bacterial pathogens.

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

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

In order to maintain study blind, all subjects will receive once daily the same total volume of study drug solution divided over 2 separate but sequential intakes at the same time of day (see Section 6 for more details).

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

Subjects will be required to have a study visit at the study site or, if feasible, at home, on Day 3, Day 8, Day 14 (±1), and Day 21 (±3). On Day 28 (±3), subjects will be contacted by site staff for a telephone follow-up visit. In case subjects are experiencing ongoing AEs or have clinically

significant laboratory abnormalities at time of the Day 21 follow-up visit, subjects might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site or, if feasible, at home on Day 28 (±3).

Study drugs will be administered orally. Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. The first dose of study drug will be administered before the subject leaves the site. On Day 1, study-site personnel can dispense to the subject all the required study drug for dosing at home, but partial dispensing at other visits is also allowed. Study-site personnel will instruct subjects on how to use and store study drug for at home dosing. Dosing should occur once daily preferably at approximately the same time each day. Study drug can be administered without regard to meals and is preferably followed by drinking a glass of water.

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

Viral resistance will be monitored by sequencing of the viral F-gene on all baseline samples and on post baseline samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at the request of the protocol virologist. Sequencing data will not be reported to the investigators (see Section 11.4.3).

Clinical course and severity of RSV infection will be assessed through different measures (see Section 9.2.2).

Pharmacokinetic assessments during the study will be based on sparse sampling and will be performed using a popPK model (see Section 9.3).

Safety and tolerability, including AEs, laboratory assessments, ECGs, physical examination, and vital signs will be assessed throughout the study from signing of the Informed Consent Form (ICF) (including diagnostic ICF, if applicable) until the subject's last study-related activity (see Section 9.7).

Medical resource utilization will be assessed (see Section 11.7).

Blood samples for host mRNA assessment may be used for exploratory biomarker analyses to determine the effects of JNJ-53718678 on markers of RSV disease at the sponsor's discretion. Leftover mid-turbinate nasal swabs and blood samples collected for other testing may be used as well for the same purpose (see Section 11.6).

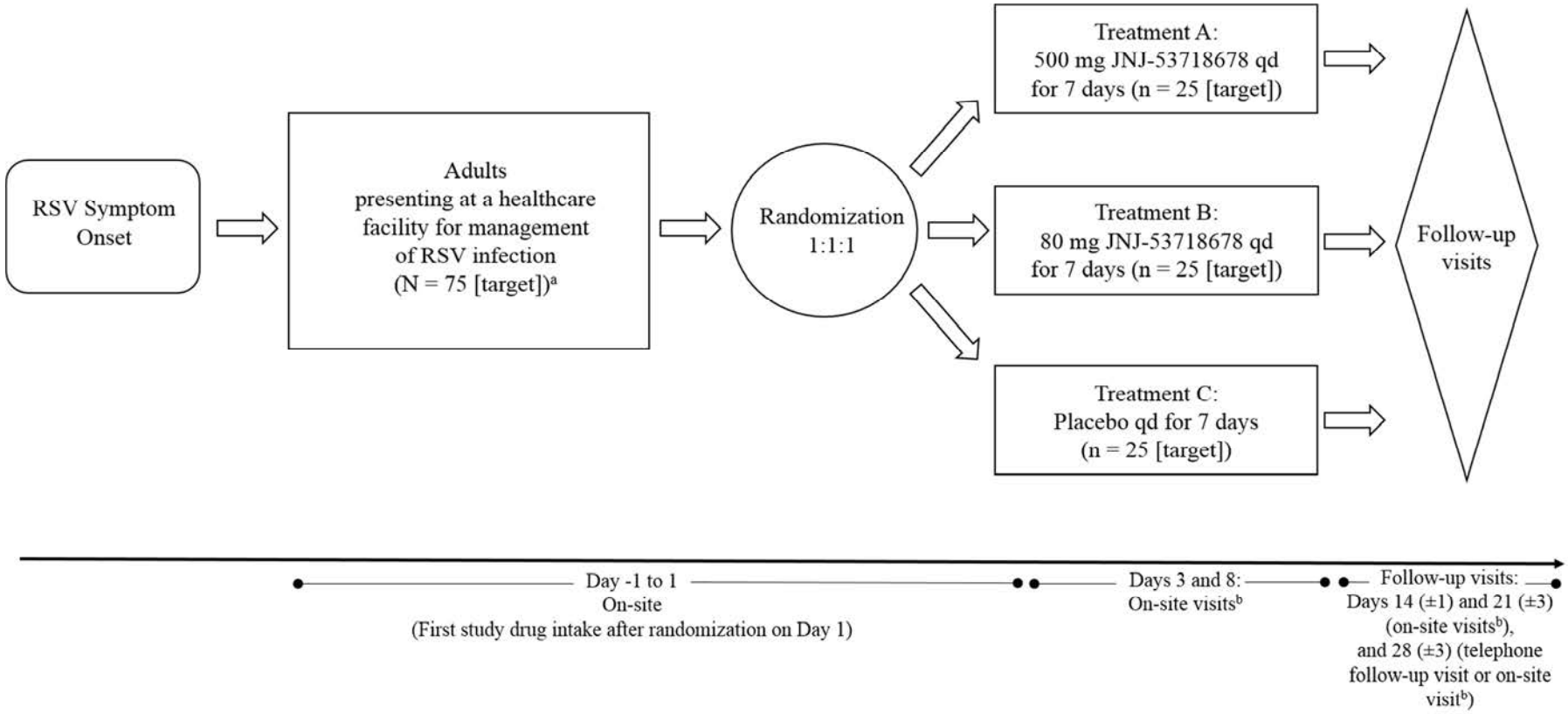
An interim analysis is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8 (see Section 11.1).

A DRC will be in place (see Section 11.9).

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a Withdrawal and a Safety Follow-up Visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered and be encouraged to attend an optional Safety Follow-up Visit.

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

Figure 1: Schematic Overview of the Study



Abbreviation: qd: once daily

[a] Subjects with symptom onset >3 days before randomization may account for maximum of 50% of all enrolled subjects.

[b] If feasible, home visits are allowed instead of on-site visits.

3.2. Study Design Rationale

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

RSV is considered the most important virus causing acute LRTI. LRTI results in substantial illness and morbidity in the elderly and adults with underlying chronic illnesses, underlying disorders of cellular immunity, or suppressed immune systems in hospitalized and community based patients.[4,10,11,12,18,19,27] In the United States alone, among patients >65 years of age, 177,000 hospitalizations and approximately 14,000 deaths per year are attributable to RSV infection.[2] In other countries, the 60-day mortality rate for adults hospitalized with RSV infection has been observed to be as high as 13.8%.[17] Currently the only available treatment for RSV is supportive and symptomatic care. As such, there is an unmet medical need for prophylactic (pre- and post-exposure) as well as therapeutic treatment in both children and adults. Disease interception at time of the initial healthcare professional (HCP) contact may shorten disease course and may prevent worsening of RSV disease, and as such also avoid the need for or shortening hospitalization.[8] Therefore, this study will be conducted in outpatients infected with RSV not in need of hospitalization.

In a previous study in healthy adult subjects infected through inoculation with a laboratory strain of RSV (study 53718678RSV2001), antiviral activity as well as an improvement in clinical symptoms of different doses of JNJ-53718678 was observed. Antiviral activity was also observed in pediatric subjects who were hospitalized due to RSV-infection (study 53718678RSV1005).

The current study is designed to explore the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics of 80 mg and 500 mg JNJ-53718678 once daily for 7 days in naturally infected adults. The study will include both subjects who are otherwise healthy (ie, without underlying condition) or who have comorbid conditions (eg, asthma, COPD, cardiovascular disease, other chronic diseases), with the exception of immunocompromised subjects, presenting for medical care but not requiring hospitalization.

Blinding, Control, Study Phase/Periods, Treatment Groups, and Stratification

There is currently no approved treatment routinely used for the treatment of RSV infection. A placebo control will be used to establish the frequency and magnitude of changes in virologic and clinical endpoints that may occur in the absence of active treatment. The use of a placebo control will allow for any AEs or laboratory abnormalities observed during the course of the study to be evaluated properly, ie, to differentiate between events potentially related to the use of JNJ-53718678 vs those related to the underlying disease.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and

baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Subjects will be randomized 1:1:1 into 3 different treatments (Treatment A [8 mL + 42 mL oral solution of JNJ-53718678], B [8 mL oral solution of JNJ-53718678 + 42 mL of matching placebo solution], and C [8 mL + 42 mL of matching placebo solution]). Subjects randomized to placebo (ie, Treatment C) will receive matching placebo for each of the doses being evaluated in the active regimens.

Randomization will be stratified by time of symptom onset (≤3 days vs >3 days before randomization). Subjects with symptom onset >3 days before randomization may account for maximum of 50% of all enrolled subjects. In another respiratory disease (flu), time since symptom onset was an important determinant of efficacy, with early (within 2 days) treatment start being more efficacious than a later start.[24] Whether the same is true for RSV remains to be established.

Population

Adult subjects of ≥18 years of age are targeted. Comorbid subjects are included as certain comorbidities are known risk factors for severe RSV disease. Outpatients are targeted as this is the population with the highest incidence of RSV infection and given that early intervention (ie, upon first HCP contact) might be beneficial in terms of clinical outcomes.

Dose Selection

The active regimens evaluated in this design are selected to provide a range of plasma concentrations of JNJ-53718678 aimed at providing information on antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics in the target population of adult subjects infected with RSV.

The doses selected for this study are based on the results of the human challenge study 53718678RSV2001, in which proof of concept for JNJ-53718678 was demonstrated. In the 53718678RSV2001 study, exposure to JNJ-53718678 resulted in a reduction of viral load over time in all three JNJ-53718678 dose groups (75, 200, and 500 mg once daily) as compared to the placebo group. Mean (± standard deviation [SD]) exposures (minimum observed concentration [C_{min}] and AUC_{24h}) observed in this study ranged between 44.3 ng/mL (±16.2) and 3,874 ng.h/mL (±831) at 75 mg and 307 ng/mL (±192) and 26,520 ng.h/mL (±7,520) at 500 mg at Day 7 (Table 1). In addition to study 53718678RSV2001, results from the interim analysis of study 53718678RSV1005 in hospitalized pediatric subjects showed antiviral activity at exposure ranges similar to exposures in adult subjects obtained in the human challenge study 537186478RSV2001. Overall, based on the currently available data, it is anticipated that the proposed doses will be in the therapeutic range of JNJ-53718678 for adults. For dosing accuracy reasons, 80 mg was selected over 75 mg as this dose results in a rounded number of volume, while still falling within the range of exposures with the 75-mg dose.

Table 1: Pharmacokinetic Results of JNJ-53718678 After Administration of 75 mg (Cohort 2), 200 mg and 500 mg JNJ-53718678 Once Daily (Cohort 1+2) in Study 53718678RSV2001

Pharmacokinetics of JNJ-53718678 (mean ± SD, t_{max}: median [range])	**75 mg JNJ-53718678 qd** (Cohort 2)	**200 mg JNJ-53718678 qd** (Cohort 1+2)	**500 mg JNJ-53718678 qd** (Cohort 1+2)
N	13[a]	17[b]	18[c]
Day 7			
C_{trough}, ng/mL	49.7 ± 16.6	84.6 ± 44.0	334 ± 197
C_{min}, ng/mL	44.3 ± 16.2	77.1 ± 45.5	307 ± 192
C_{max}, ng/mL	355 ± 91.1	827 ± 203	2,184 ± 604
t_{max}, h	2.00 (0.50 – 4.02)	2.00 (0.98 – 4.00)	3.98 (1.08 – 4.00)
AUC_{24h}, ng.h/mL	3,874 ± 831	8,362 ± 1,920	26,520 ± 7,520
C_{avg}, ng/mL	161 ± 34.6	349 ± 80.2	1,103 ± 314
Fluctuation index, %	194 ± 38.8	218 ± 42.0	173 ± 26.0

[a] N = 15 for C_{max}, t_{max} and AUC_{24h} on Day 1, N = 14 for C_{trough} on Day 3, Day 5 and Day 6, and for the dose-normalized pharmacokinetic parameters on these days.
[b] N = 15 for C_{trough}, and $C_{trough,dose\ normalized}$ on Day 5, N = 16 for all pharmacokinetic parameters of Day 6 and Day 7.
[c] N = 17 for all pharmacokinetic parameters of Day 7.
qd: once daily; C_{avg}: average plasma concentration at steady-state over the dosing interval

Study Duration

Dosing will last for 7 days as data have shown that the duration of viral shedding upon RSV infection is at least that long. In addition, this was also the duration of dosing in the healthy volunteer challenge study in adults (study 53718678RSV2001), which was generally safe and well tolerated (see Section 1.1) and the same dosing duration is being investigated in the ongoing study 53718678RSV1005 in pediatric subjects.

Biomarker Collection

Blood samples for host mRNA assessment will be collected at time points indicated in the TIME AND EVENTS SCHEDULE and may be used for exploratory biomarker analyses (eg, proteins including cytokines), on the premise that these markers may play a role in the treatment response, safety or pharmacokinetics of JNJ-53718678, or RSV-related disease. Leftover mid-turbinate nasal swabs and blood samples collected for other testing may be used as well for the same purpose. Analyses of biomarkers will be conducted at the sponsor's discretion and may be reported separately from this study.

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

No human DNA analysis will be performed.

Medical Resource Utilization Data Collection

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

Interim Analysis

An interim analysis is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8 as planned per the TIME AND EVENTS SCHEDULE. The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the interim results and other ongoing studies of JNJ-53718678.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible after presentation to the healthcare facility, such that subjects are randomized (within a maximum of 5 days after RSV symptom onset) and treatment is initiated as soon as possible (but no later than 4 hours after randomization).

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

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

4.1. Inclusion Criteria

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

1. Male or female.

2. ≥18 years of age.

   Note: If the legal age of consent in the jurisdiction in which the study is taking place is >18 years, this respective legal age is binding for eligibility.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.2. Exclusion Criteria

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

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

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

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

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

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

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

6. Subject has known allergies, hypersensitivity, or intolerance to JNJ-53718678 or to any of the excipients of the JNJ-53718678 or placebo formulation (refer to the IB[15]).

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

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

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

10. Women who are pregnant or breastfeeding.

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

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

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

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

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

16. Subjects who received an investigational vaccine at any time prior to the study, or an investigational drug, or used an invasive investigational medical device within 30 days or 5 elimination half-lives (whichever is longer) prior to screening or is currently

enrolled in an investigational study.

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

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

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).

2. Agree to the daily completion of the patient-reported outcomes, additional questions, study medication and concomitant medication log, swabbing log, and temperature log.

3. Concurrent administration of medications/use of licensed devices is allowed as supportive therapy per local standard of care, as long as the medication/licensed device will not affect the subject’s participation in the study and is in accordance with allowed concomitant therapy.

   Refer to Section 8 for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 3 treatments (Treatments A to C; 1:1:1 randomization). Randomization will be 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 by time since symptom onset at randomization (≤3 days and >3 days). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

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

6. DOSAGE AND ADMINISTRATION

The subjects will receive the treatments as described in Table 2. Study drugs will be administered orally.

Table 2: Treatment Overview

Treatment	Dosing Regimen	Volume and Formulation
A	500 mg JNJ-53718678 once daily for 7 days	8 mL + 42 mL oral solution of JNJ-53718678[a]
B	80 mg JNJ-53718678 + matching placebo once daily for 7 days	8 mL oral solution of JNJ-53718678[a] + 42 mL of matching placebo solution
C	placebo once daily for 7 days	8 mL + 42 mL matching placebo solution

[a] JNJ-53718678 is formulated as an oral solution containing 10 mg/mL of active drug substance (G024). The matching placebo consists of the oral vehicle solution without active drug substance (G026).

Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. Study drug administration should occur once daily at approximately the same time each day. JNJ-53718678/placebo can be administered without regard to meals and is preferably followed by drinking a glass of water. Each dosing day, the same total volume of study drug solution should be administered, ie, 50 mL, divided over 2 separate but sequential intakes (1 container with 8 mL and 1 container with 42 mL).

On Day 1, date and time of dosing will be captured by the site staff in the eCRF. At home, date and time of dosing will be captured in the study medication log, to be completed by the subject in the electronic device. On Day 3 and Day 8 (days with pharmacokinetic sampling), the time of the meal, if any within 2 hours before or after dosing, will also be recorded in the study medication log.

Study-site personnel will instruct subjects on how to store study drug for at home use as indicated for this protocol.

7. TREATMENT COMPLIANCE

On Day 1, study drug will be administered orally at the study site.

In case of vomiting, the subject should not be redosed.

In case a dose was missed, the dose should be given as soon as possible but within 12 hours after the scheduled time. If more than 12 hours have elapsed, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule.

8. CONCOMITANT THERAPY

Concomitant medications, except those listed below, are allowed during this study. All concomitant medications and supportive therapy are to be recorded in the eCRF, as well as in the source documents, from the date the ICF is signed through to the end of study visit. The dosage, route of administration, frequency, start and stop dates, and the indication should be noted in the source documentation and the eCRF.

Subjects will be required to document use of concomitant medication in the electronic medication log from signing of the ICF until the last study visit, which will serve as source document for the site staff to complete the eCRF.

Subjects can receive medications such as acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs, or antihistamines, taking into account their respective package insert, at the investigator's discretion.

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

- Inhaled β-agonists or anticholinergics (also permitted as maintenance therapy for the underlying asthma or COPD);
- Inhaled corticosteroids and, to a certain extent, systemic corticosteroids (see below);
- Oral/intravenous/intramuscular antibiotics such as β-lactams and azithromycin.

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

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

- Herbal supplements with active metabolic enzyme inducing components (eg, St-John's Wort) within 21 days prior to randomization and during the study with the exception of topically administered products;
- The following prescription medications:

- Macrolide antibiotics (with the exception of azithromycin).
- Systemic corticosteroids if used for >7 consecutive days immediately prior to randomization at doses higher than 20 mg/day of prednisone or equivalent. Subjects meeting the eligibility criteria at screening but requiring increased doses of systemic corticosteroids (>20 mg/day of prednisone or equivalent) for a prolonged period (>7 consecutive days) during the study are allowed to continue participating in the study.
- Prescription medications used within 14 days prior to randomization and during the study with an antiviral effect on RSV to treat the RSV infection itself (eg, inhaled/oral ribavirin, intravenous RSV immunoglobulin). Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.
- Prescription medications which are known to be a strong inducer or a strong inhibitor of CYP3A4 enzymes, such as, but not limited to, erythromycin, clarithromycin, ritonavir, and rifampin, within 14 days prior to screening and during the study or CYP3A substrates with narrow therapeutic index such as, but not limited to, anti-arrhythmics (amiodarone, disopyramide, flecainide, mexiletine, systemic lidocaine, propafenone, quinidine), antihistamines (astemizole, terfenadine), or gastrointestinal/ gastroesophageal reflux disease drugs (cisapride).

- Any other investigational drug within 30 days or 5 elimination half-lives of that drug (whichever is longer) prior to screening and during the study;
- Any investigational vaccine, including investigational RSV vaccines, at any time prior to and during the study;
- JNJ-53718678 prior to screening.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of antiviral effect, clinical course, safety, pharmacokinetic, biomarker, and MRU assessments applicable to this study.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG, vital signs, clinical parameters, blood sampling, and physical examination. Actual dates and times of assessments will be recorded in the source documentation and CRF.

Medical resource utilization data will be collected. Refer to Section 9.6, for details.

The maximum amount of blood drawn from each subject for study-specific purposes will not exceed 450 mL over the duration of the study.

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

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

9.1.2. Screening Phase

The procedures specified in the TIME AND EVENTS SCHEDULE will only be performed after written informed consent has been obtained.

Screening will be completed and randomization will be performed within a maximum of 5 days after the onset of RSV symptoms to ensure the eligibility of the subject. Procedures that are standard of care and performed within approximately 48 hours prior to randomization may be used in determining study eligibility.

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected at screening and analyzed at the central laboratory. Subjects can start treatment before the laboratory results are available. In case abnormalities as described in Section 10.2 are observed in the blood samples collected at screening after the subject has started treatment, treatment may need to be discontinued.

During screening, one mid-turbinate nasal swab will be collected for:

- RSV diagnosis using a rapid PCR-based (preferably locally available) or rapid-antigen-detection test. In case the test detects more than one virus, the subject is eligible as long as RSV is one of the viruses detected.
- RSV diagnosis confirmation using a PCR-based assay post-hoc (at the central laboratory).
- Examination for the presence of other viruses or bacteria using multiplex PCR post-hoc (at the central laboratory).

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

A clinical evaluation will be performed. This includes but is not limited to respiratory rate, heart rate, SpO_2, and body temperature (measured by the same method and preferably by the same person throughout the study). In addition, to evaluate RSV symptoms' presence and severity, subjects will have to complete the RI-PRO, answer the additional questions about health and functioning, and subjects enrolled after approval of this amendment will also have to complete the RiiQ Symptom Scale. Subjects will have to rate their HRQOL by completing the 5-level EuroQol 5-Dimension (EQ-5D-5L), and subjects enrolled after approval of this amendment will also have to complete the RiiQ Impact Scale.

9.1.3. Double-Blind Treatment Phase

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

Day 1/Day of Randomization

Eligible subjects will be randomized on Day 1. Study drug administration should start as soon as possible, but no later than 4 hours after randomization, which should occur within a maximum of 5 days after RSV symptom onset. Subjects will receive the first dose of study drug on Day 1 at the healthcare facility. Date and time of dosing will be captured by the site staff in the eCRF.

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

Day 2 to Day 8 (End of Treatment)

Study drug administration continues until 7 doses have been taken. Subjects will receive 7 doses in total without regard to meals, administered once daily preferably at approximately the same time as on Day 1 each day. Study drug administration is preferably followed by drinking a glass of water. On Day 1, study-site personnel can dispense to the subject all the required study drug for dosing at home, but partial dispensing at other visits is also allowed. Study-site personnel will instruct subjects on how to use and store study drug for at home dosing. Date and time of dosing will be captured in the study medication log, to be completed by the subject in the electronic device.

Assessments will be performed as detailed in the TIME AND EVENTS SCHEDULE.

Telephone calls to the subjects to facilitate compliance with study procedures between outpatient study visits are permitted.

9.1.4. Posttreatment Phase (Follow-Up)

Day 9 to Day 28(±3)

Subjects will be evaluated for a total of 28 days post randomization. Subjects will be required to return to the healthcare facility as an outpatient or, if feasible, have a home visit scheduled, for follow-up assessments on Day 14 and Day 21 as indicated in the TIME AND EVENTS SCHEDULE. On Day 28, subjects will be contacted by site staff for a telephone follow-up visit. In case subjects are experiencing ongoing AEs or have clinically significant laboratory abnormalities at time of the Day 21 follow-up visit, subjects might be requested, at the discretion of the investigator, to have a safety follow-up visit at the site or, if feasible, at home on Day 28. On Day 28 all subjects will complete the study. Assessments will be performed as indicated in the TIME AND EVENTS SCHEDULE.

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a Withdrawal and a Safety Follow-up Visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered and be encouraged to attend an optional 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. Assessments will be performed as indicated in the TIME AND EVENTS SCHEDULE.

9.2. Efficacy Evaluations

9.2.1. Antiviral Activity

As an evaluation of antiviral activity, the RSV viral load in nasal secretions, obtained via mid-turbinate nasal swab, will be measured at the central lab using a qRT-PCR assay. Mid-turbinate swab specimens for the determination of RSV viral load will be collected at several time points during the study as indicated in the TIME AND EVENTS SCHEDULE. Mid-turbinate swabs should be collected from the same nostril throughout the study (unless precluded due to bleeding). It will be collected in the eCRF or the electronic device (for home swabs) which nostril was sampled.

The first mid-turbinate nasal swab should be collected as close as possible and prior to the first administration of study drug (on Day 1). The next swabs (from Day 2 to Day 8) should be collected preferably at approximately the same time as on Day 1 each day. On Day 8, the investigator will check whether the subject is still symptomatic. For asymptomatic subjects swabbing will be stopped. For subjects still symptomatic, swabbing will be continued daily until the subject becomes asymptomatic or until Day 13 at the latest. Whether a subject is still symptomatic will be checked with daily telephone calls between the subject and site staff (and/or by review of the transmitted ePRO data) in case swabbing is performed by the subject (or his/her spouse, partner, relative, or other caregiver) or by an HCP other than investigational site staff. On Day 14 and Day 21, a swab will be collected during the scheduled visit. During scheduled visits on Day 1, Day 3, Day 8, Day 14, and Day 21, swabs must be collected by an HCP (investigator/study-site personnel). On the other days, mid-turbinate swabs are collected at home preferably by an HCP and, only if not possible by an HCP, by the subject (or his/her spouse, partner, relative, or other caregiver) after being properly trained by the investigator/study-site personnel. In case preferred by the subject, all mid-turbinate swabbing may also be performed at the site.

The sampling should be documented in the electronic device or the eCRF (for the sampling at the scheduled visits).

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

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

If feasible, the RSV infectious virus titers as measured by quantitative culture of RSV (plaque assay) on selected nasal swab samples, may also be assessed.

9.2.2. Clinical Severity and Clinical Course of RSV Infection

The following evaluations of the clinical course of RSV infection will be performed throughout the study as indicated in the TIME AND EVENTS SCHEDULE:

- Clinical parameters: respiratory rate, heart rate, SpO_2, and body temperature as measured during site visits. Subjects will be provided a thermometer and asked to record body temperature in the electronic device as indicated in the TIME AND EVENTS SCHEDULE.
- Evolution and severity of signs and symptoms of RSV disease as assessed by the subject on a hand-held electronic device using the RI-PRO, the RiiQ Symptom Scale (if the subject was enrolled after approval of this amendment) and additional questions about health and functioning. Symptoms reported in the RI-PRO or RiiQ Symptom Scale will not be reported as AEs but constitute a part of the efficacy evaluations. Subjects will also complete the EQ-5D-5L and the RiiQ Impact Scale (for subjects who were enrolled after approval of this amendment) on the electronic device to rate their HRQOL.
- Need for hospitalization or medically attended visits (other than the study mandated visits) during treatment and follow-up.

9.2.3. Viral Sequencing

Viral resistance will be monitored by sequencing of the F-gene of the viral genome on all baseline samples and on post baseline samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at the request of the protocol virologist. Sequencing data will not be reported to the investigators.

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

9.3. Pharmacokinetics

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.

Venous blood samples for determination of JNJ-53718678 plasma concentrations will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE. Samples can also be used for the analysis of metabolites of JNJ-53718678, excipients (eg, hydroxypropyl-β-cyclodextrin), 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 pharmacokinetics 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. Subject confidentiality will be maintained.

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

Based on the individual concentration-time data, using the actual dose taken and the actual sampling times, pharmacokinetic parameters and exposure information of JNJ-53718678 will be

derived using popPK modelling, including, but not limited to: AUC, C_{trough}, and possibly C_{max}. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant. Other pharmacokinetic parameters may be determined at the discretion of the sponsor if deemed useful to evaluate the pharmacokinetics 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.

The following times need to be recorded on the requisition form and/or the study medication log: date and time of study drug intake, date and time of pharmacokinetic blood sampling, and time of meal if any in the time window of 2 hours before and 2 hours after study drug intake on the day of pharmacokinetic sampling.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Obtained pharmacokinetic and pharmacodynamic data (selected antiviral activity parameters, clinical outcomes, and safety parameters) will be used to explore the relationship between the pharmacokinetics and pharmacodynamics.

9.5. Biomarkers

Blood samples for host mRNA assessment will be collected at time points indicated in the TIME AND EVENTS SCHEDULE and may be used for exploratory biomarker analyses (eg, proteins including cytokines), on the premise that these markers may play a role in the treatment response, safety or pharmacokinetics of JNJ-53718678, or RSV-related disease. Leftover mid-turbinate nasal swabs and blood samples collected for other testing may be used as well for the same purpose. Analyses of biomarkers will be conducted at the sponsor's discretion and may be reported separately from this study.

9.6. Medical Resource Utilization

Medical resource utilization data will be collected in the eCRF for all subjects throughout the study at time points indicated in the TIME AND EVENTS SCHEDULE. Protocol-mandated procedures, tests, and encounters are excluded. The data collected will include:

- Number and duration of medical care encounters: hospitalizations, physician or emergency room visits, test, and procedures, including surgeries, and other procedures (inpatient and outpatient) for RSV infection or complications associated with RSV per investigator assessment.

9.7. Safety Evaluations

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

Details regarding the DRC are provided in Section 11.9.

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

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

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

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12. Grading will be determined according to the criteria specified in the DMID adult toxicity tables (see Attachment 1).

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

Exacerbations of underlying pulmonary disease (eg, asthma, COPD) occurring after treatment start, 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). Further details on these events of interest will be captured separately in the eCRF.

Evaluations of signs and symptoms of RSV disease that are part of the efficacy evaluations (with exception of the complications mentioned above) will not be reported as AEs.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected at time points indicated in the TIME AND EVENTS SCHEDULE and analyzed at the central laboratory. 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. Laboratory reports must be filed with the source documents.

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

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

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -RBC count
  -WBC differential:
  * neutrophils
  * lymphocytes

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

Note: A 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.

- Coagulation parameters: PT, aPTT and international normalized ratio
- Serum Chemistry Panel

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

- Urinalysis

Dipstick
-specific gravity
-pH
-glucose
-protein
-blood
-ketones
-bilirubin
-urobilinogen
-nitrite
-leukocyte esterase

Sediment (if dipstick result is abnormal)
-RBC
-WBC
-epithelial cells
-crystals
-casts
-bacteria

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

- Renal function testing:
  - Serum creatinine and estimated Glomerular Filtration Rate (eGFR) based on creatinine by Cockcroft-Gault formula[25]
  - Serum cystatine C and eGFR based on cystatine C[25]

  - Urinary creatinine, albumin, *N*-acetyl-β-glucosaminidase, β_2-microglobulin, urinary phosphorus, sodium, potassium, and calcium (spot urine sample)
- Urine pregnancy testing for all women

Electrocardiogram

Twelve-lead triplicate ECGs will be collected at the time points specified in the TIME AND EVENTS SCHEDULE and when clinically indicated.

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

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

In the event that an invasive procedure such as a blood draw or nasal aspirate and an ECG are required at the same time, ECGs should be collected first. Electrocardiograms may be repeated at the investigator's discretion to account for erroneous readings.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Vital Signs

Systolic and diastolic blood pressure are to be collected at the time points specified in the TIME AND EVENTS SCHEDULE.

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

Blood pressure measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Clinically relevant abnormalities occurring during the study should be recorded by the investigator in the AE section of the eCRF.

Physical Examination

A physical examination (including height [only at screening] and body weight measurements) and skin examination will be performed at the visits indicated in the TIME AND EVENTS SCHEDULE.

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

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

Specific Toxicities

Rash

In case there are skin changes, a correct diagnosis has to be made by the investigator or a dermatologist, preferably within 24 hours of detection. If a diagnosis of rash is made, the investigator will discuss this with the sponsor, preferably within 24 hours of the investigator's awareness of the rash. An assessment of severity grade should be made using the criteria specified in the DMID adult toxicity tables (see Attachment 1).

If the rash is considered to be most likely due to RSV, concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

If a causal relationship between the rash and the study drug is reasonably suspected, then the visits and assessments will be performed as indicated in Attachment 5. Unscheduled follow-up visits for close follow-up of rash will be performed based on the grade (severity) of the rash. At the investigator's discretion, additional visits and assessments can be performed.

AST and ALT Evaluation

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

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

Grade 1 (1.1 to <2.0 x upper limit of normal [ULN]), or Grade 2 (>2.0 to ≤3.0 x ULN)

Subjects may continue the intake of study drug.

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

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

Subjects will permanently discontinue the intake of study drug.

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

9.8. Other Evaluations

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

9.9. Sample Collection and Handling

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

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

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

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

10.1. Completion

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

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

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

A subject's study treatment must be discontinued if:

- The subject withdraws consent.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.

- The subject has a confirmed QTcF interval >500 ms at the Day 3 visit, per the machine read parameter result. Confirmation needs to be obtained during the visit by repeat triplicate ECG recording.
- The subject is reported with the following laboratory abnormalities: AST or ALT increases ≥3 x ULN at screening, confirmed in a repeat test, to be performed within 48 hours of the result being available at the site.
- The subject is reported with any other laboratory abnormality of grade 3 or 4, except for grade 3 or 4 elevations of triglycerides, low density lipoprotein cholesterol, and/or cholesterol at screening, confirmed in a repeat test, to be performed within 48 hours of the result being available at the site.

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule, or, at a minimum, to return to the site for a Withdrawal and a Safety Follow-up Visit. Subjects who withdraw consent during the treatment or follow-up phase will be offered and be encouraged to attend an optional 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.

Withdrawal From the Study

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

- Lost to follow-up.
- Withdrawal of consent.
- Death.
- The subject is poorly compliant with study procedures, study drug administration, visits, and assessments, after evaluation and discussion between the investigator and sponsor.
- Decision by the sponsor to stop or cancel the study.
- Decision by the investigator to withdraw subjects.
- Decision by local regulatory authorities and Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) to stop or cancel the study.

Subjects who withdraw consent during the follow-up phase will be offered an optional Safety Follow-up Visit. At the Safety Follow-up Visits, the same assessments as on the Day 21 visits will be performed.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

10.3. Withdrawal From the Use of Research Samples

A subject 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 subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for exploratory biomarker research, 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 Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

11.1. Interim Analysis

An interim analysis, encompassing efficacy, safety, and pharmacokinetics is planned after at least 36 subjects have been dosed and have completed the assessments of Day 8 as planned in the TIME AND EVENTS SCHEDULE. Enrollment will not be paused during the interim analysis.

Investigators, subject(s) and local sponsor representatives will remain blinded. The central sponsor team members will be unblinded at time of the interim analysis.

Further details regarding the interim analysis will be specified in an interim SAP.

The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the results and other ongoing studies of JNJ-53718678 (see Section 11.9). The DRC will consist of senior sponsor personnel outside of the central sponsor team and not involved in study conduct.

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

The primary (final) analysis will be performed after the last subject has completed his/her last visit of the study.

11.2. Subject Information

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

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

11.3. Sample Size Determination

The interim results (estimates of mean AUC and change from baseline of RSV viral load ±SD) of study 53718678RSV1005 were the basis of the sample size calculation. In that study, median (range) time to onset of symptoms was 5 (2-12) days and baseline viral load was 5.3 (2.1-8.3) $\log_{10}$ copies/mL.

For the AUC viral load from Day 1 to Day 7, a (placebo) point estimate of 490 and an SD of 135 $\log_{10}$ copies x hr/mL was observed for the AUC viral load from Day 1 to Day 7. The sample size was determined in order to obtain estimates of the mean AUC viral load with a precision of approximately 50 $\log_{10}$ copies x hr/mL of the true value with 90% confidence; with 20 subjects per treatment group the half-width of the 90% confidence would be approximately 52 and with 24 subjects per treatment group the precision would be approximately 47 $\log_{10}$ copies x hr/mL.

For the change from baseline (on Day 2 or Day 3), (placebo) point estimates of -0.11 and -0.33 and SDs of 1.85 and 1.56 $\log_{10}$ copies/mL, respectively, were observed. The observed difference (active versus placebo) was -1 to -2 $\log_{10}$ copies/mL. With an assumed SD of 1.85 $\log_{10}$ copies/mL, 20 subjects per treatment group will lead to a precision (90% confidence interval [CI] half width) of 0.986 and 24 subjects per treatment group to a precision of 0.896 $\log_{10}$ copies/mL for the estimate of the difference between active dose and placebo .

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

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

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

11.4. Efficacy Analyses

The primary population for the efficacy/antiviral activity analysis will be the intent-to-treat infected population consisting of all randomized subjects who received at least one dose of study treatment and who have a central lab-confirmed RSV infection.

11.4.1. Antiviral Effect

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

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

If feasible, the RSV infectious virus titers as measured by quantitative culture of RSV (plaque assay) on selected nasal swab samples, may also be assessed.

Endpoints will be analyzed graphically and descriptively as described in the SAP. For continuous variables descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For viral efficacy parameters also 90% CIs will be computed comparing active dose groups versus placebo. For categorical variables, frequency tables will be presented. Kaplan-Meier Curves will be produced to graphically describe the time to event data.

To explore the antiviral effect, $\log_{10}$ 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, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors over time. The differences in the AUCs for active versus placebo will be derived using

appropriate contrasts deriving least squares mean differences, including the 90% 2-sided CIs. Details will be provided in the SAP.

Additional analyses will be performed to investigate other endpoints, including exploratory endpoints. Details on these analyses will be provided in the SAP.

11.4.2. Clinical Severity and Clinical Course of RSV Infection

All data from PRO questionnaires for the assessment of the subject's severity of RSV symptoms, health and functioning, and HRQOL (see Section 9.2.2) will be summarized descriptively by treatment group.

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

11.4.3. Viral Sequencing

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

11.5. Pharmacokinetic Analyses

Population pharmacokinetic analysis of concentration-time data of JNJ-53718678 will be performed using nonlinear mixed-effects modelling. An updated popPK model will be developed with the current adult data combined with those of selected Phase 1 studies to support a relevant structural model. Available subject characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting pharmacokinetic parameters. This updated model will be used for the final pharmacokinetic parameters estimation for each subject with available data. For each dose, descriptive statistics including arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum of the final pharmacokinetic parameters (AUC, C_{trough}, and possibly C_{max}) will be provided. The pharmacokinetic analyses will be detailed in an analysis plan. Analyses of other analytes (eg, excipients, metabolites) may be performed at the discretion of the sponsor.

A snapshot date for pharmacokinetic samples to be analyzed for the planned interim analysis will be defined. Samples collected before this snapshot 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 interim analysis database lock.

Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetics (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for pharmacokinetic parameter calculation).

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

For each treatment group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived pharmacokinetic parameters including exposure information of JNJ-53718678.

11.6. Other Analyses

Biomarker Analyses

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

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 pharmacokinetic/pharmacodynamic analyses may be presented in a separate report.

11.7. Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group.

11.8. Safety Analyses

Safety data will be presented descriptively. No statistical testing of safety data is planned. For safety, baseline is defined as the last assessment prior to the first intake of study drug.

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

Adverse Events

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

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience an AE of at least grade 3, or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test and by treatment. Descriptive statistics of absolute values and changes from baseline will be calculated for each laboratory analyte at baseline and at each scheduled time point.

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

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

Urinary renal function parameters will be analyzed for the analyte as well as for the analyte ratio over urinary creatinine.

Laboratory abnormalities will be tabulated by scheduled time point.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations.

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: QT corrected according to Bazett's formula, and QTcF.[1,12,14,23]

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

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).

The percentage of subjects with abnormalities (as defined in Attachment 4) will be tabulated by treatment.

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits (as defined in Attachment 4) will be summarized by treatment.

Physical Examination

Physical examination findings and changes from baseline will be listed at each scheduled time point.

11.9. Data Review Committee

A DRC, comprised of senior sponsor personnel outside of the central sponsor team and not involved in study conduct, will be established. The DRC will monitor safety data during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring.

After the review of the accumulating safety data from this study, the DRC will make recommendations regarding the continuation of the study.

The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the interim results and other ongoing studies of JNJ-53718678. Given the challenges of ensuring study site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the changes recommended by the study team and endorsed by the DRC will be communicated in writing to investigators, health authorities, and IECs/IRBs and will be implemented without amendment to this protocol.

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

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal

relationship with the treatment. 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 Council for 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 (diagnostic, if applicable) ICF (refer to Section 12.3.1 for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

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

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

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

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

12.2. Special Reporting Situations

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

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

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 SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

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

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Signs and symptoms of RSV disease, such as rhinitis, rhinorrhea, nasal congestion, sneezing, nasopharyngitis, earache, malaise (tiredness), cough, shortness of breath and/or wheezing, muscle and/or joint pain, headache, fever, nasal blood spotting, and decreased oxygen saturation are part of the efficacy-related assessments and hence should not be reported as AEs.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the IEC/IRB that approved the protocol

unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

12.3.2. Serious Adverse Events

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

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed 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 made by facsimile (fax).

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

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or HCP 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 subject'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 subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the study drug may have an effect on sperm, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any post-natal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

JNJ-53718678 supplied for this study is formulated as an oral solution containing 10 mg/mL JNJ-53718678-AAA drug substance, HP-β-CD, acetic acid, sodium hydroxide, concentrated hydrochloride acid, sucralose, strawberry flavor, and purified water. It will be manufactured and provided under the responsibility of the sponsor.

The matching placebo consists of the oral vehicle solution without active drug substance. The placebo solution will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

JNJ-53718678 and placebo will be packed in appropriate containers under responsibility of the sponsor. Multiple containers will be required to cover the entire dose schedule.

Secondary packaging will be child-resistant to accommodate outpatient use.

Packaging and labeling of JNJ-53718678 and placebo will be done in a double-blind way.

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

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Handling and Storage

All study drug should be stored on site in the original package at controlled temperatures ranging from 2°C to 8°C. It will be advised to also store the study drugs at temperatures between 2°C to 8°C at the subjects' homes.

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

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- JNJ-53718678 IB and any addenda.
- Pharmacy manual/study site investigational product and procedures manual.
- Laboratory manual.
- Electronic device for assessments of patient-reported symptoms and functioning, EQ-5D-5L, and for recording of study and concomitant medication, temperature, and swabbing in the respective logs and completion guidelines.
- Thermometers for subjects to measure body temperature at home during treatment and follow-up.

- Specimen collection kits for pharmacokinetic, safety blood, and urine samples and mid-turbinate nasal swabs.
- Contact information page(s).
- Dose dispensing instructions.
- IWRS manual.
- eCRF and ePRO/logs completion guidelines.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. 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 they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be acceptable.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the subjects).
- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved subject recruiting materials.

- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug.
- New information that may adversely affect the safety of the subjects or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths of subjects under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject 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.

Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of nasal mid-turbinate swabs by signing the pre-screening (diagnostic) ICF if such testing is not standard of care at the investigational site.

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

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

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining

all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the subject (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 his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-53718678, to understand RSV infection, to understand differential drug responders, and to develop tests/assays related to JNJ-53718678 and RSV infection. The research may begin at any time during the

study or the post-study storage period. No human genetic testing will be performed on these samples.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, 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) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

The central sponsor team members will review the unblinded interim efficacy, safety, and pharmacokinetic analyses and will make recommendations to the DRC regarding possible changes to the design of the study: dropping the lower dose, changing the stratification factor (and/or the requirement of maximum 50% of all enrolled subjects with symptom onset >3 days before randomization), changing the maximum number of days between RSV symptom onset and randomization and/or the number of time points/visits for collecting a nasal swab by HCP. The DRC will decide on the implementation of the recommendations based on the review of the interim results and other ongoing studies of JNJ-53718678. Given the challenges of ensuring study site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the changes recommended by the study team and endorsed by the DRC will be communicated in writing to investigators, health authorities, and IECs/IRBs and will be implemented without amendment to this protocol.

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

in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with those commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data may be recorded directly into the eCRF and will be considered source data:

- Race.
- History of smoking and all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum.
- Blood pressure and heart rate.
- Height and weight.
- Details of physical examination.

The minimum source documentation requirements for Section 4.1 and Section 4.2 that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

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

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Patient-Reported Assessments

Patient-reported assessments (see Attachment 2, Attachment 3, Attachment 6, and Attachment 7) will be completed on an electronic device provided to the subject at the study-site. Responses provided will be recorded directly in the electronic database.

The subject will provide information about his/her health status, symptoms, and functional status, as well as on his/her HRQOL, on an electronic device at time points noted in the TIME AND EVENTS SCHEDULE. In addition, the subject will record study drug intake on the electronic device in medication logs. The date and time of nasal swabs collected at home during the study will also be recorded on the electronic device in a swabbing log. The subject will also complete temperature logs at home. All subject self-assessments and logs will be provided in the native language of the subject. The electronic device will include instructions and training that will be completed upon first use by the subject (or by the subject's spouse, partner, relative, or friend) and will be available on demand thereafter if the subject chooses this option. If the subject is unable to complete the assessments on the electronic device, the subject's spouse, partner, relative, or friend who has completed the training on use of the electronic device can read the questions and response options aloud to the subject and enter the subject's responses in the electronic device on the subject's behalf. At screening and on Day 1, if the subject is unable to complete the assessment on the device and the subject's spouse, partner, relative, or friend is not available to enter the subject's responses on the device for the subject, trained study-site personnel can read the questions and response options to the subject and record the subject's responses on the device on the subject's behalf. Investigational staff will regularly (preferably daily) review the completion of the assessments of patient-reported symptoms and functioning and the logs once data is transmitted from the electronic device and contact the subject in case there are issues identified with completion of the assessments.

17.7. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.8. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, and all study documents as specified by the

applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.9. Monitoring

The sponsor will use a combination of monitoring techniques as specified in the monitoring guidelines 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/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.

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.10.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study drug development.

17.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.12. Use of Information and Publication

All information, including but not limited to information regarding JNJ-53718678 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including 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. Results of 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. Results of the viral sequencing analysis may be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Toxicity Tables

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE[20] – NOVEMBER 2007

ABBREVIATIONS: Abbreviations utilized in the Table:

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

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	**Mild** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	**Moderate** Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe** Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

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

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization [WHO]) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/l	> 7.0 mEq/ L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/d L	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany

CHEMISTRIES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/d L	>15.0 mg/d L
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	>6 x ULN or dialysis required

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

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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 50% - 70% (of peak flow)	no normalization with bronchodilator; FEV1 25% - 50% of peak flow; or retractions present	cyanosis: FEV1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring oxygen therapy

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

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

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

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

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

Attachment 2: Respiratory Infection-Patient Reported Outcomes (RI-PRO ©) Symptom Questionnaire

We would like to know about the symptoms you have been experiencing during the past 24 hours. For each symptom, please mark one box ☐ under the response that best matches your experience. Mark the "Not at all" box, if you did not have that symptom in the past 24 hours.

What time is it? _____ AM / PM (please circle)

Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Runny or dripping nose	☐	☐	☐	☐	☐
Congested or stuffy nose	☐	☐	☐	☐	☐
Sinus pressure	☐	☐	☐	☐	☐
Scratchy or itchy throat	☐	☐	☐	☐	☐
Sore or painful throat	☐	☐	☐	☐	☐
Difficulty swallowing	☐	☐	☐	☐	☐
Teary or watery eyes	☐	☐	☐	☐	☐
Sore or painful eyes	☐	☐	☐	☐	☐
Eyes sensitive to light	☐	☐	☐	☐	☐
Trouble breathing	☐	☐	☐	☐	☐
Chest congestion	☐	☐	☐	☐	☐
Chest tightness	☐	☐	☐	☐	☐
Dry or hacking cough	☐	☐	☐	☐	☐
Wet or loose cough	☐	☐	☐	☐	☐
Felt nauseous (feeling like you wanted to throw-up)	☐	☐	☐	☐	☐
Stomach ache	☐	☐	☐	☐	☐

Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Felt dizzy	☐	☐	☐	☐	☐
Head congestion	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐
Lack of appetite	☐	☐	☐	☐	☐
Sleeping more than usual	☐	☐	☐	☐	☐
Body aches or pains	☐	☐	☐	☐	☐
Weak or tired	☐	☐	☐	☐	☐
Chills or shivering	☐	☐	☐	☐	☐
Felt cold	☐	☐	☐	☐	☐
Felt hot	☐	☐	☐	☐	☐
Sweating	☐	☐	☐	☐	☐

In the past 24 hours, how often have you had any of the following symptoms?

	Never	Rarely	Sometimes	Often	Always
Sneezing	☐	☐	☐	☐	☐
Coughing	☐	☐	☐	☐	☐
Coughed up mucus or phlegm	☐	☐	☐	☐	☐

	0 times	1 time	2 times	3 times	4 or more times
How many times did you vomit?	☐	☐	☐	☐	☐
How many times did you have diarrhea?	☐	☐	☐	☐	☐

Attachment 3: Additional Questions About Health and Functioning

Adult RSV Additional Questions[a]

For each of the following questions please select one response only

1. Did you take any medicine for your respiratory infection symptoms today?
   - ☐ Yes
   - ☐ No

2. Did you use any rescue medicine today for asthma or COPD?
   - ☐ I do not take medicine for asthma or COPD
   - ☐ Yes
   - ☐ No

3. Since this time yesterday, how much of the time did you breathe oxygen from an oxygen tank?
   - ☐ None of the time
   - ☐ Less than an hour
   - ☐ 1 to 4 hours
   - ☐ More than 4 hours

4. Overall, how severe were your respiratory infection symptoms today?
   - ☐ No respiratory infection symptoms today
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very Severe

5. Overall, how were your respiratory infection symptoms today compared to yesterday?
   - ☐ Much better
   - ☐ Somewhat better
   - ☐ A little better
   - ☐ About the same
   - ☐ A little worse
   - ☐ Somewhat worse
   - ☐ Much worse

6. How much did your respiratory infection symptoms interfere with your usual activities today?

   - ☐ Not at all
   - ☐ A little bit
   - ☐ Somewhat
   - ☐ Quite a bit
   - ☐ Very much

7. Have you returned to your usual activities today?

   - ☐ Yes
   - ☐ No

8. In general, how would you rate your physical health today?

   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Fair
   - ☐ Poor

9. Have you returned to your usual health today?

   - ☐ Yes
   - ☐ No

[a] Questions 1, 2,-4-9 adapted for RSV from the FLU-PRO User Manual; question 3 adapted from Janssen Observational Protocol NOPRODRSV0004.

Attachment 4: Cardiovascular Safety - Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

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

NAP = not applicable
For absolute QTc parameters the categories are defined based on the ICH E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	**Diastolic blood pressure**	**Systolic blood pressure**
Abnormalities on actual values			
Abnormally low	≤ 45 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥ 100 mmHg - < 110 mmHg	≥ 160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.
[b] The classification of AEs related to hypotension and hypertension will be done according to the DMID grading scale.

Attachment 5: Visit Schedule for Rash Management for Adult Subjects

This visit schedule summarizes the visits and assessments to be performed in case of rash. At the investigator's discretion, additional visits and assessments can be performed.

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 1 of rash[1]	• Study medication may be continued. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (preferably within 24h). • Referral to dermatologist (preferably within 24h) **ONLY IF** rash diagnosis or relationship with study medication is uncertain.	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (preferably within 24h). • Referral to dermatologist (preferably within 24h) **ONLY IF** rash diagnosis or relationship with study medication is uncertain.	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (within 24h). • Referral to dermatologist **REQUIRED** (preferably within 24h). • At the discretion of the investigator or at request of the dermatologist, assessment of safety blood sample. • Biopsy **ONLY IF** required by dermatologist.
Day 2	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED**.	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED**.	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**.
Day 3	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At the discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 4	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At the discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 5	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At the discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 6	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At the discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 7	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	No rash follow-up visit required.
Day 8	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED**.	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED.**	No rash follow-up visit required.
Further Visits	If rash is unresolved after second follow-up visit, further visits (with digital pictures) at the investigator's discretion.[2]	If rash is unresolved after second follow-up visit, further visits (with digital pictures) at the investigator's discretion.[2]	Weekly follow-up visits **REQUIRED** (with digital pictures) until resolution of grade 3-4 rash to grade ≤2 rash (further follow-up visits according to grade 1 or grade 2 rash instructions).

[1] Note that Day 1 of the rash is the first day of investigator assessment and not the first day of rash as reported by the subject and that the following days are in relation to this first assessment (not study days).

[2] In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3, or 4 rash as appropriate.

Attachment 6: 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

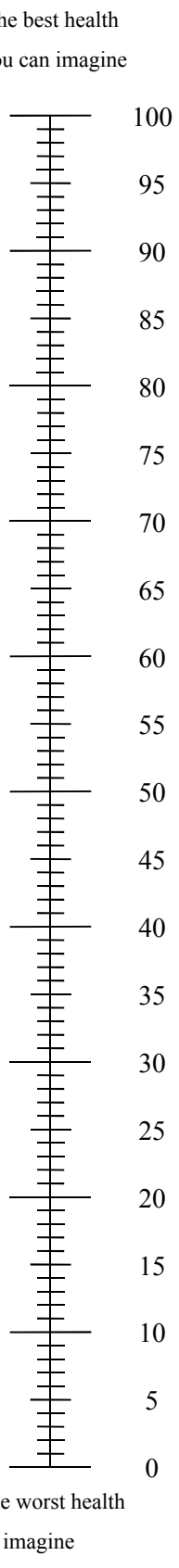
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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

YOUR HEALTH TODAY = ☐



Attachment 7: Respiratory Infection Intensity and Impact Questionnaire (RiiQ)

Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)[a]

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

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

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

[a] Respiratory Infection intensity and impact questionnaire (RiiQ™) ©RH Osborne (2006, 2018) . No part of the RiiQ™ may be copied or reproduced in any form without written permission from Richard Osborne PhD : measuredsolutions@bigpond.com (Variable recall Version. English. Administered under license by Janssen Pharmaceuticals).

[b] Either 12 hour or 24 hour recall will be used as specified in the TIME AND EVENTS SCHEDULE.

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

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

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

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

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

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

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 drug, 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): Maria-Rita Stevens

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol 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.

SIGNATURES

Signed by	Date	Justification
Rekha Sinha	24Apr2019, 16:09:42 PM, UTC	Document Approval by Delegation