Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Clinical Outcomes, Antiviral Activity, Safety, Tolerability, Pharmacokinetics, and Pharmacokinetics/Pharmacodynamics of JNJ-53718678 in Adult and Adolescent Hematopoietic Stem Cell Transplant Recipients with Respiratory Syncytial Virus Infection of the Upper Respiratory Tract

FREESIA

Effects of JNJ-53718678 in Adult and Adolescent Patients Who had a Hematopoietic Stem Cell Transplantation and Who are Infected With RSV

Protocol 53718678RSV2005; Phase 2
AMENDMENT 6

JNJ-53718678

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	7 May 2021
Amendment 5	03-Aug-2020
Amendment 4	10-Jul-2020
Amendment 3	03-Jun-2020
Amendment 2	11-Dec-2019
Amendment 1	21-Jun-2019
Original Protocol	7-Jun-2019

Amendments below are listed beginning with the most recent amendment.

Amendment 6 (7 May 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is to replace the oral suspension formulations of JNJ-53718678 and placebo by oral film-coated tablets based on supportive data from Study 53718678RSV1011, for newly enrolled participants after implementation of Protocol Amendment 6.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedules of Activities 2.2 Background 4.1 Overall Design 4.3.1 Study Intervention Dose 5.2 Exclusion Criteria 6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 6.4 Study Intervention Compliance 8.1 Overview	The oral suspension (supplied as powder and solvent) of JNJ-53718678 and placebo are replaced by oral film-coated tablets for all newly enrolled participants after implementation of Protocol Amendment 6.	The switch from the oral suspension to the oral film-coated tablet is based on supportive bioavailability and safety data from Study 53718678RSV1011. Additionally, oral film-coated tablets are more patient-friendly for the adolescent and adult population in this study compared to the oral suspension.
1.3 Schedules of Activities	The Day 1 and Day 3 ECGs and Day 1 and Day 15 sparse PK sampling were changed from approximately 1 hour into approximately 1 to 1.5 hours after JNJ-53718678 intake under fasted conditions, for both hospitalized participants and outpatients.	A window between 1 and 1.5 hours after drug intake was introduced to cover both oral suspension and oral tablet formulations, which have a median T_{max} between 1 and 1.5 hours.
10.12 Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic	Wording was added to specify the clinical management of laboratory-confirmed SARS-CoV-2 infection, diagnosed during the study, in participants, ie, per local standard of care.	Clarification

Section Number and Name	Description of Change	Brief Rationale
5.3 Lifestyle Considerations 6.6 Concomitant Therapy 10.12 Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic	Specifics were added on the administration of a locally approved (including emergency use-authorized) COVID-19 vaccine during the study.	Additions were made per recent Health Authority guidance.
6.6 Concomitant Therapy	Guidance was added with regard to participants who receive seasonal (eg, influenza) or other routine vaccinations during the study.	Clarification
1.3 Schedules of Activities 5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation	Participants with ≥Grade 3 laboratory abnormality of hypokalemia of <2.5 mEq/L and/or hypomagnesemia of <0.9 mEq/L at Screening (or 4 days prior to Screening) will be excluded from the study. Language in other relevant protocol sections was aligned with these changes.	The wording regarding QT-related safety measures was made more specific to and more stringent for clinically relevant (≥Grade 3) hypokalemia and hypomagnesemia.
1.1 Synopsis 9.3 Sample Size Determination 9.4.2.1Primary Endpoint: Development of RSV Lower Respiratory Tract Infection 9.4.2.2 Key Secondary Endpoints 11 REFERENCES	Log-binomial model was changed to stratified Cochran-Mantel-Haenszel test for analysis of the primary endpoint and key secondary endpoints on the proportion of participants hospitalized, and proportion of participants progressing to respiratory failure and/or death.	Stratified Cochran-Mantel-Haenszel test is preferred instead of log-binomial model to analyze the binary outcomes. There is a known risk of non-convergence with log-binomial models and methods to overcome the non-convergence might result in biased estimates of the treatment effect.
1.3 Schedules of Activities 4.1 Overall Design 7.1 Discontinuation of Study Intervention	A recommendation was added for participants who prematurely discontinue study intervention for any reason, ie, to remain compliant to all study-related procedures including timely completion of all efficacy assessments up to Day 49 or at least through Day 28.	To reduce the amount of missing data from participants who prematurely discontinue study intervention.
9.4.2.3 Clinical Course of RSV Infection	The total length of hospital stay was removed from the time-to-event variable examples.	Correction of error. The total length of hospital stay is not considered a time to-event variable but a duration variable (see Amendment 2) since participants might not be hospitalized as of the beginning of the study, and even could switch between in-and outpatient status over the course of the study. This endpoint will be analyzed using a Hodges-Lehmann test.

Section Number and Name	Description of Change	Brief Rationale
10.12 Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic	The following updates were made: • The blood sample for RSV viremia was removed from the Day 1 home visit assessments. • The requirement for dry ice provision for transport of RSV viremia blood samples was removed.	Correction of errors.
Throughout	Minor corrections and updates were done throughout.	

Amendment 5 (03 August 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to implement recommendations by Health Authorities (HA).

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedules of Activities 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation 10.2 Appendix 2: Clinical Laboratory Tests	It was clarified that levels of potassium and magnesium should be determined by the local and by the central laboratory.	Clarification. All safety laboratory assessments are being done by the central laboratory to maintain uniformity of assay. Some assessments are also performed locally when quick turnaround time is necessary for medical decision making.
2.3.3 Benefit-Risk Assessment for Study Participation	It was clarified that close monitoring of hypokalemia and hypomagnesemia and corrective actions in case of laboratory abnormalities for these analytes is also applicable at Screening.	Correction of inconsistency.
2.3.3 Benefit-Risk Assessment for Study Participation 8.3.3 Electrocardiograms 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation	It was clarified throughout that the cardiac safety management refers to QTcF interval changes.	Correction of inconsistency.
5.2 Exclusion Criteria	Exclusion criterion #24 was added to exclude participants with a personal or family history of long QT syndrome or sudden cardiac death.	Part of QT prolongation mitigation measures to ensure participants' safety.
5.2 Exclusion Criteria	Exclusion criteria #19.1 and #22 were combined in exclusion criterion #19.2 as they were almost identical.	Correction of redundancy.

Amendment 4 (10 July 2020)

Overall Rationale for the Amendment: The overall reason for the amendment is to implement recommendations by Health Authorities (HA).

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 8.3.3 Electrocardiograms	A clarification was added to specify the timing of ECG monitoring on Day 1 and Day 3 (steady state) to be performed at t_{max} of JNJ-53718678 (time to reach C_{max}), ie, approximately 1 hour (fasted) or approximately 4 hours (fed) post dose.	Given that potential QT prolongation is C_{max} related, as observed in the TQT study 53718678RSV1009, timing of the ECG is more specifically aligned with the timing of expected C_{max} both after the first dose and at steady state, in line with recommendations by HA.
2.3.3 Benefit-Risk Assessment for Study Participation 7.1 Discontinuation of Study Intervention 8.3.3 Electrocardiograms 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation	The study intervention discontinuation and withdrawal criterion specific to ECG QT interval changes was adapted from values >500 ms to values ≥500 ms.	In line with recommendations by HA.
6.6 Concomitant Therapy	The BCRP inhibitors eltrombopag, rolapitant, fostamatinib, teriflunomide, and curcumin were added to the disallowed concomitant therapy section.	JNJ-53718678 is a substrate for BCRP based on in vitro data. Clinically relevant BCRP inhibitors are prohibited to avoid potential DDI with JNJ-53718678, in line with recommendations by HA.
6.6 Concomitant Therapy	Removal of azithromycin as generally allowed medication.	Correction to an oversight of the previous amendment related to disallowed concomitant medications with QT-prolonging effects. Azithromycin is a QT prolonging drug allowed with restrictions.
Throughout	Minor corrections and clarifications were done throughout.	

Amendment 3 (03 June 2020)

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

Section Number and Name	Description of Change	Brief Rationale
2.2 Background 2.3.1.2 Potential Risks 2.3.3 Benefit-Risk Assessment for Study Participation 4.3.1 Study Intervention Dose	The important potential risk of QT interval prolongation identified in the TQT study was added.	New potential risk identified from a TQT study and reflected in the relevant sections of the protocol.
2.2 Background 2.3.2.1 Known Benefits 2.3.2.2 Potential Benefits 2.3.3 Benefit-Risk Assessment for Study Participation	Recently available relevant clinical data were included in the introduction. Accordingly, the Investigator's Brochure Addendum to Edition 06 was added as a reference.	New relevant clinical data available and reflected in the relevant sections of the protocol.
1.1 Synopsis 1.2 Schema 1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 4.1 Overall Design 4.3.1 Study Intervention Dose 6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 6.4 Study Intervention Compliance 6.6 Concomitant Therapy 8.5 Treatment of Overdose	Dose regiment was adjusted to 250 mg bid for participants with no co-administration of strong or moderate CYP3A4 inhibitors. The period during the study when certain concomitant medications are disallowed was aligned with the 3 days wash out period of the study intervention. The definitions of missing dose and overdose were adapted accordingly.	The daily dosing frequency was changed from qd to bid dosing while maintaining the total daily dose (ie, at each intake half of the total daily dose will be administered). The proposed bid dosing will ensure the highest potential antiviral effect while minimizing the risk of development of resistance, as well as mitigating the important potential risk of QT interval prolongation. The $t_{1/2}$ of JNJ-53718678 is approximately 10 hours therefore the study intervention is washed out after 3 days.
1.1 Synopsis 1.2 Schema 1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 4.1 Overall Design 4.3.1 Study Intervention Dose 6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 6.5 Dose Modification 6.6 Concomitant Therapy	For participants with coadministration of moderate or strong CYP3A4 inhibitors with the exception of posaconazole, the dose of the study intervention was reduced to 125 mg bid.	PBPK data indicate potential for increase of the C_{max} due to CYP3A4 inhibition. With a dose reduction to 125 mg bid when moderate or strong CYP3A4 inhibitors are coadministered, this increase in C_{max} remains below the threshold for the potential QT-prolongating effect.
1.1 Synopsis 1.2 Schema 1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 4.1 Overall Design 4.3.1 Study Intervention Dose	For participants with coadministration of posaconazole, the dose of the study intervention was reduced to 125 mg qd.	JNJ-53718678 steady-state exposure (AUC) after 250mg bid dosing without concomitant use of CYP3A4 inhibitors is similar to that after 125 mg qd dosing with coadministration of

Section Number and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 6.5 Dose Modification 6.6 Concomitant Therapy		posaconazole (400 mg bid) and similar to that of 125 mg bid dosing with coadministration of voriconazole (200 mg bid), clarithromycin (500 mg bid), or itraconazole (200 mg qd).
1.3.4 PK Assessments 8.6 Pharmacokinetics	Timing of PK samples was changed.	PK sampling was optimized to obtain a PK sample around expected C_{max} of JNJ-53718678 and a PK sample to collect information related to C_{trough} in view of the bid regimen.
1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 8.3.3 Electrocardiograms	The frequency of ECG monitoring was increased by adding measurements at Days 1, 8, and 15 to enhance the cardiac-related safety follow up. Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period. Details on ECG collection were added.	Part of risk mitigation plan to ensure participant's safety.
2.3.3 Benefit-Risk Assessment for Study Participation	Close monitoring of the use of concomitant medications to be conducted regularly was added.	Part of risk mitigation plan to ensure participant's safety.
2.3.3 Benefit-Risk Assessment for Study Participation 5.2 Exclusion Criteria	Specific cardiovascular and ECG-based criteria were added for eligibility assessment.	Part of risk mitigation plan to ensure participant's safety.
2.3.3 Benefit-Risk Assessment for Study Participation 7.1 Discontinuation of Study Intervention 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation	The study intervention discontinuation criteria specific to QTc interval changes were aligned with the increased frequency of ECG assessments.	Part of risk mitigation plan to ensure participant's safety.
2.3.3 Benefit-Risk Assessment for Study Participation 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation	Specific toxicity management for confirmed QTc interval value >500 ms was added.	Part of risk mitigation plan to ensure participant's safety.
1.3 Schedules of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 8.4.7.2 Cardiac Events Potentially Related to QT Prolongation 10.2 Appendix 2: Clinical Laboratory Tests	Specific guidance for the management of hypokalemia and/or hypomagnesemia was added.	Part of risk mitigation plan to ensure participant's safety.
1.1 Synopsis 1.3.3 Long-term Follow-up 4.1 Overall Design 4.4 End of Study Definition 8.10 Medical Resource Utilization	Longer term follow-up was implemented.	Sponsor decision to collect information on longer term RSV-related clinical outcomes and medical resource utilization.

Section Number and Name	Description of Change	Brief Rationale
9 STATISTICAL CONSIDERATIONS 9.4.9 Health Economics		
4.2.6 Study-Specific Ethical Design Considerations	The total blood volume was adapted to 'maximum approximately' 110 mL.	Adaptation to account for variability in the actual taken amount of blood.
8.2.1.2 Lower Respiratory Tract Samples	'for RSV' was added to central testing of lower respiratory tract sample.	A clarification was added that the central testing that may be provided is for testing of RSV.
1.3 Schedules of Activities 4.1 Overall Design 8.2.3 Antiviral Activity	A sentence was added to indicate that another upper respiratory tract sample than the study-specific bilateral mid-turbinate nasal swab sample can also be used to perform local testing for RSV detection at Day 28, if needed based on the local PCR- or other molecular-based diagnostic assay.	A clarification was added that an upper respiratory tract sample other than the study-specific bilateral mid-turbinate nasal swab sample can also be used for local testing of RSV detection at Day 28 to align with local SOC sampling and testing.
7.1 Discontinuation of Study Intervention 8.4.7 Management of Adverse Events of Interest 8.4.7.1 Rash Management 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	Rash Management was removed.	The specific Rash Management section, which is a therapeutic area-specific section that can be adapted based on emerging data, was removed as data from both adult and pediatric studies have not indicated a rash-related safety signal.
8.6.1 Substudy in Hospitalized Participants	Removal of requirement of standardized breakfast prior to study intervention intake on intensive PK day.	For practical reasons and to collect information on PK in both fed and fasted state.
1.1 Synopsis 1.3 Schedules of Activities 7.2 Participant Discontinuation/Withdrawal From the Study 8.9 Biomarkers	A sentence was added to indicate that collection of biomarker research samples is mandatory, unless local regulations require these samples to be optional.	A clarification for the collection of blood samples for biomarker research was added to accommodate for local regulations for collection of research samples.
9.4.3 Safety Analyses	A sentence was added to indicate tabulation or listing of central/local laboratory results and local ECGs.	For clarification.
9.4.8 Other Analyses	A correction was made to 'Day 1 predose'.	A correction was done to align with Section 8.2.3.
10.9 Appendix 9: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)	The RiiQ Impact Scale was updated.	The latest copyrighted RiiQ version was used for the appendix.
1.3 Schedules of Activities 4.1 Overall Design 5.1 Inclusion Criteria 5.2 Exclusion Criteria 10.12 Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic	COVID-19-related measures were added to provide guidance on study conduct during the COVID-19 pandemic.	COVID-19 pandemic ongoing at time of amendment writing.
Throughout	Minor corrections and clarifications were done throughout.	

Amendment 2 (11 December 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is to ensure consistency between different sections, to clarify, and make minor corrections to different parts of the protocol. In addition, regulatory feedback from competent authorities was incorporated.

Section Number and Name	Description of Change	Brief Rationale
Throughout	The references to the Investigator's Brochure (IB) in the text were updated to "the most recent IB". The reference to the IB was updated to the newest version (Edition 6).	More straightforward to refer to the most recent IB in the text and specify current version in the reference.
Throughout	Minor grammatical, formatting, or spelling changes were made throughout the protocol.	To correct for minor errors that were noted in the protocol.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The wording "is discarded" was added to the secondary endpoint "Total length of hospital stay (time in hospital before first dosing is discarded) and total time in the intensive care unit (ICU) (time in ICU before first dosing is discarded)".	Alignment for consistency with wording in Efficacy Analyses in Synopsis and Section 9.4.2.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The definition of the abbreviation RiiQ was added to the footnote of the "Objectives and Endpoints" table.	The definition was added for clarification.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The wording "as determined by the EAC" was added to the definition of respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI).	Added for completeness.
1.1 Synopsis 8.9 Biomarkers	The wording "or other clinical outcomes in this population" was removed from the sentence "Analyses of biomarkers may be conducted at the sponsor's discretion and reported separately from this study".	Wording was introduced by mistake.
1.1 Synopsis 9.4.2.2 Key Secondary Endpoints	The method for analyzing the key secondary endpoints total length of hospital stay and the number of supplemental O_2 free days was adapted from Gehan-Wilcoxon test to Hodges-Lehmann test.	The Gehan-Wilcoxon test is more suitable for time-to-event data (time to resolution of symptoms). The duration parameters (total length of hospital stay and the number of supplemental O_2 free days) will be analyzed using the Hodges-Lehmann test.
1.2 Schema	The schematic overview of the study was updated to include inclusion criterion #4 (ALC <1,000 cells/μL).	The schematic overview of the study was updated for completeness.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedules of Activities	In Section 1.3.2. (Schedule of Activities for Outpatients), provision of study intervention for daily use at home on Day 3 was removed.	Correction. Outpatients are not provided with study intervention for daily use at home on Day 3. They receive 2 bottles covering 6 days of dosing on Day 1.
1.3 Schedules of Activities 5.1 Inclusion Criteria 8.1 Overview 10.2 Appendix 2: Clinical Laboratory Tests	"Local" was added to all pregnancy testing, including the serum pregnancy test at screening. Accordingly, the wording "by the central laboratory" was removed from the sentence "The following tests will be performed according to the Schedule of Activities" in Appendix 2.	Clarification that the pregnancy test is to be performed locally.
1.3.1 Hospitalization Through Discharge	The Schedule of Activities for hospitalized participants was adjusted (Day 35 and Day 49).	Adjusted to clarify which assessments are only to be performed in case abnormalities are observed at Day 28.
1.3.3 PK Assessments 8.6.1 Substudy in Hospitalized Participants	The footnotes of Table 1 and Table 2 in Section 1.3.3 were adjusted. The sentence "Participants in the rich serial PK sampling substudy will not participate in the sparse PK study" in Section 8.6.1 was removed from the protocol and the header of Table 1 in Section 1.3.3 was adjusted accordingly.	Adjusted to clarify timing of sampling. Correction, participants in the rich serial PK sampling substudy will also participate in the sparse PK study.
4.3 Justification for Dose and Duration	A justification for the selected dosing regimen in adolescents has been added.	Requested by regulatory authorities.
5.1 Inclusion Criteria	Inclusion criterion #14 was updated to add the required duration for males to use contraception, ie, from Day 1 and for 90 days after receiving the last dose of study drug.	Requested by regulatory authorities.
6.5 Concomitant Therapy	In the concomitant therapy section, the section on disallowed prescription medications within 14 days prior to Screening and during the study was updated. Ciprofloxacin, atazanavir, and darunavir were removed from the list of prohibited strong Cytochrome P450 (CYP)3A4 inhibitors. Ciprofloxacin was added to the examples of allowed moderate CYP3A4 inhibitors. Telithromycin, nefazodone, posaconazole, nelfinavir, saquinavir, and erythromycin were removed from the list of prohibited strong CYP3A4 inhibitors. The note "In Study 53718678RSV1009 (Thorough QT Study) and other clinical studies, exposures several fold above the 500 mg exposure have not led to any safety concerns. Strong CYP3A4 inhibitors posaconazole, telithromycin, ceritinib, nefazodone, nelfinavir, saquinavir, conivaptan, ribociclib, idelalisib, and boceprevir are allowed, as their effect on JNJ-53718678 exposure is expected to be less than 2-fold" was added.	Ciprofloxacin, atazanavir, and darunavir are considered moderate CYP3A4 inhibitors based on the University of Washington Drug Interaction Database (DIDB).[30] The list of CYP34 inhibitors by DIDB was used as guidance for disallowed and allowed strong CYP3A4 inhibitors. Based on DIDB, CYP isoforms inhibitors are identified and classified based on the available area under the plasma concentration-time curve (AUC) ratios of clinical index substrates, sensitive substrates, and moderate sensitive substrates, recommended by the FDA drug-drug interactions (DDI) guidance.[20]

Section Number and Name	Description of Change	Brief Rationale
		In Study 53718678RSV1006, JNJ-53718678 was coadministered with itraconazole (a strong CYP3A4 and P-gp inhibitor) and no safety signal was identified. $AUC_{0-\infty}$ of JNJ-53718678 increased 3.45-fold. Based on the DIDB, itraconazole increases midazolam exposure by 10.80 fold (effect of size itraconazole on JNJ-53718678 is 0.32 compared to midazolam [3.45/10.80]). Based on these clinical data, it can be calculated for the list of strong CYP3A4 inhibitors that the increase in plasma exposure of JNJ-53718678 is 2-fold or less due to concomitant administration of posaconazole, telithromycin, ceritinib, nefazodone nelfinavir, saquinavir, conivaptan, ribociclib, idelalisib, and boceprevir. Inclusion of these strong CYP3A4 inhibitors is deemed acceptable. Strong CYP3A4 inhibitors such as mibefradil, clarithromycin, tipranavir/ritonavir (rtv), ritonavir, cobicistat, ketoconazole, troleandomycin, telaprevir, danoprevir/rtv, elvitegravir/rtv, saquinavir/rtv, itraconazole, and indinavir are disallowed.
	Addition of a note with respect to voriconazole.	Voriconazole is considered a strong CYP3A4 inhibitor, but is allowed as comedication based on additional physiologically based PK analysis (PBPK) analysis, showing a moderate effect on JNJ-53718678 AUC of 2.86-fold.
7.1 Discontinuation of Study Intervention 7.2 Participant Discontinuation/Withdrawal From the Study	The sentence “At the Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 28 and Day 35 visits, respectively, will be performed” was corrected to “Day 22 and Day 28”.	Alignment between text in Schedules of Activities and Sections 7.1 and 7.2.

Section Number and Name	Description of Change	Brief Rationale
8.2.6 Evaluation of RSV Viremia	The word "respiratory" was removed from the sentence "At the discretion of the sponsor, these samples may also be used for exploratory analysis of other respiratory pathogens in plasma that may play a role in treatment response, safety, or the status and/or course of RSV-related disease or other clinical outcomes in this population.".	Alignment for consistency with Section 4.1 and Section 8.2.1.4.
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Update to clarify that all adverse events (AEs), whether serious or non-serious, whether anticipated or not anticipated, will be recorded and reported.	Clarification following regulatory authorities request.
8.4.4 Regulatory Reporting Requirements for Serious Adverse Events	Rhinitis was removed from the list of Anticipated Events (Table 5).	Correction. Rhinitis will not be monitored as an anticipated event.
8.4.4 Regulatory Reporting Requirements for Serious Adverse Events	Update to clarify that also individual anticipated serious adverse events (SAEs) will be reported appropriately, according to the requirements of the countries in which the study is conducted.	Clarification following regulatory authorities request
8.4.6 Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events	Update to clarify that if symptoms of RSV disease are considered related to the drug intervention or meet the definition of seriousness, they will be reported as an AE/SAE accordingly.	Requested by regulatory authorities.
10.2 Appendix 2: Clinical Laboratory Tests	The term creatinine clearance was replaced by $eGFR_{crea}$.	$eGFR_{crea}$ is a more accurate terminology when referring to CKD-EPI formula for determination of creatinine clearance.
10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The protocol was updated to better align Section 10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, with the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (10.7 Appendix 7).	For consistency between Section 10.4 Appendix 4 and DMID Adult Toxicity Table (Section 10.7 Appendix 7), as requested by regulatory authorities.
10.5 Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Update to remove tubal occlusion/ligation from the list of permanent sterilization methods while retaining it in the list of acceptable contraception for this study.	Alignment with guidance related to contraception and pregnancy testing in clinical trials from the Clinical Trials Facilitation and Coordination Group of the European Heads of Medicines Agencies, as requested by regulatory authorities.[27]

Amendment 1 (21 June 2019)

Overall Rationale for the Amendment: The overall reasons for this amendment are to correct for an inconsistency with regard to the classification of CYP3A4 inhibitors and CYP3A4 inducers in the concomitant therapy section and to update the exclusion criteria to clarify that enrollment of participants during the follow-up phase of another clinical study is allowed.

Section Number and Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy	In the concomitant therapy section, the section on disallowed prescription medications within 14 days prior to Screening and during the study was updated. Cyclosporin and glucocorticoids were removed from the list of prohibited strong CYP3A4 inhibitors and CYP3A4 inducers, respectively, and added to the examples of allowed moderate CYP3A4 inhibitors and CYP3A4 inducers, respectively. Posaconazole was added to the list of prohibited strong CYP3A4 inhibitors. Voriconazole and isavuconazole were added to the list of moderate CYP3A4 inhibitors, which are allowed.	The concomitant therapy section of the protocol was updated because cyclosporin and glucocorticoids were incorrectly listed as a strong CYP3A4 inhibitor and strong CYP3A4 inducers, respectively. The antifungal drugs posaconazole, voriconazole, and isavuconazole, were added for completeness, as these are used in the target population. ***Note:*** Voriconazole, which is a moderate/strong CYP3A4 inhibitor, is allowed based on additional physiologically based PK analysis (PBPK).
5.2 Exclusion Criteria 6.5 Concomitant Therapy	Exclusion criteria 12 and 16 were updated. In exclusion criterion 12, a note that concurrent enrollment is allowed during the follow-up phase of another clinical study, was added. In exclusion criterion 16, the term investigational drug and its related note were removed as this is covered in exclusion criterion 12. The concomitant therapy section was updated for consistency with exclusion criterion 16.	These exclusion criteria were updated to clarify that enrollment of participants during the follow-up phase of another clinical study is allowed, given the frequent participation of HSCT recipients in other investigational treatment studies with long follow-up periods.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Clinical Outcomes, Antiviral Activity, Safety, Tolerability, Pharmacokinetics, and Pharmacokinetics/Pharmacodynamics of JNJ-53718678 in Adult and Adolescent Hematopoietic Stem Cell Transplant Recipients with Respiratory Syncytial Virus Infection of the Upper Respiratory Tract

Effects of JNJ-53718678 in Adult and Adolescent Patients Who had a Hematopoietic Stem Cell Transplantation and Who are Infected With RSV

JNJ-53718678 is an investigational, potent small-molecule respiratory syncytial virus (RSV)-specific fusion inhibitor belonging to the indole chemical class which targets the F-protein and prevents the conformational changes of the F-protein required for fusion of the viral envelope with the host cell membrane, thereby inhibiting viral replication and syncytia formation.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the effect of JNJ-53718678 on the development of RSV lower tract respiratory infections (LRTIs) in adult hematopoietic stem cell transplant (HSCT) recipients with RSV upper respiratory tract infection (URTI).	The proportion of participants who develop RSV LRTI (see definition below) per the Endpoint Adjudication Committee (EAC)'s assessment through Visit Day 28.
Secondary	
To evaluate the effect of JNJ-53718678 on the development of RSV-associated lower respiratory tract complications (LRTC) in adult and adolescent HSCT recipients with RSV URTI.	The proportion of participants who develop RSV-associated LRTC (see definition below) per the EAC's assessment through Visit Day 28.
To evaluate the safety and tolerability of JNJ-53718678	Safety and tolerability, as assessed by AEs, clinical laboratory testing, electrocardiograms (ECGs), vital signs, throughout the study
To evaluate the impact of JNJ-53718678 on progression to respiratory failure and on all-cause mortality	• The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death, in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment; • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death (all-cause mortality); • The proportion of participants progressing to death (all-cause mortality), in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment;

Objectives	Endpoints
	• The proportion of participants progressing to death (all-cause mortality); • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive), in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment; • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive).
To evaluate the impact of JNJ-53718678 on the clinical course of RSV infection	Clinical course-related endpoints: • Number of supplemental O_2 free days through Day 28 • Incidence of O_2 requirement, total length and type (eg, supplemental oxygen, noninvasive pressure ventilation, invasive mechanical ventilation [tracheal tube, laryngeal mask, or tracheostomy]) • Respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) over time as measured by the investigator during scheduled visits • Proportion of participants hospitalized (of participants who were not hospitalized at baseline), proportion of participants re-hospitalized (of participants who were hospitalized at baseline and discharged during the study and of participants who were not hospitalized at baseline, required hospitalization, and were discharged during the study) • Total length of hospital stay (time in hospital before first dosing is discarded) and total time in the intensive care unit (ICU) (time in ICU before first dosing is discarded) • Incidence of Grade 3 and Grade 4 adverse events (AEs) in the Infections and Infestations System Organ Class • Incidence of respiratory and thoracic-related AEs • Incidence of antibiotic use in participants who develop and in those who do not develop RSV

Objectives	Endpoints
	LRTI or RSV-associated LRTC per the EAC's assessment • Time to resolution of symptoms, assessed through an instrument for patient-reported symptoms (Respiratory Infection Intensity and Impact Questionnaire [RiiQ] Symptom Scale) • Change from baseline through Day 28 in severity of symptoms reported by subjects in the RiiQ Symptom Scale • Time to resolution of respiratory illness, through the Patient Global Impression of Severity (PGI-S) Scale • Change in Patient Global Impression of Health (PGI-H) and Patient Global Impression of Change (PGI-C) Scales through Day 28
To evaluate the PK of JNJ-53718678	PK parameters of JNJ-53718678
To evaluate the relationship between the PK of JNJ-53718678 and the PD (selected antiviral activity, clinical outcomes, and safety parameters) after repeated dosing of JNJ-53718678	PK/PD analysis of plasma concentration-time data of JNJ-53718678 using (non)-linear mixed-effects modeling
To evaluate the antiviral effect of JNJ-53718678 as measured by RSV viral load in bilateral mid-turbinate nasal swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay	Virologic parameters derived from the RSV viral load as measured by a qRT-PCR assay in bilateral mid-turbinate nasal swab samples including: • RSV viral load and change from baseline over time • RSV viral load area under the curve (AUC) from immediately prior to first dose of study intervention (baseline) through Day 8, Day 11, Day 15, Day 22, and Day 28 • time to undetectable RSV viral load • proportion of participants with undetectable RSV viral load at each time point throughout the study
To evaluate the impact of RSV and its treatment on health-related quality of life (HRQOL).	Change from baseline for the HRQOL through Day 28 (as assessed through the 5-level EuroQol 5-Dimension [EQ-5D-5L] and RiiQ Impact Scales]
To evaluate the emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678	Changes from baseline in the RSV F-gene sequence (and potentially other regions of the RSV genome, at the discretion of the sponsor's virologist)

Objectives	Endpoints
Exploratory	
The exploratory objectives are to evaluate: • medical resource utilization (MRU), including hospitalization, for clinical management of participants during treatment and posttreatment follow-up • the RSV infectious virus titer as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay) • the relationship between antiviral activity and clinical course • the impact of the baseline RSV viral subtype and genotype on the antiviral activity and clinical course • the incidence of RSV viremia • the incidence of graft-versus-host disease (GVHD) or graft failure	The exploratory endpoints are: • MRU • RSV viral subtype and presence of pretreatment RSV F-gene polymorphisms • virologic parameters derived from the RSV viral load as measured by quantitative viral culture • proportion of participants with RSV viremia (RSV viral load in plasma) • proportion of participants with new onset GVHD • proportion of participants with graft failure

EAC: Endpoint Adjudication Committee; ECG: electrocardiogram; EQ-5D-5L: 5-level EuroQol 5-Dimension; GVDH: graft-versus-host disease; HRQOL: health-related quality of life; LRTC: lower respiratory tract complication(s); LRTI: lower respiratory tract infection; MRU: medical resource utilization; PD: pharmacodynamic(s); PGI-C: patient global impression of change; PGI-H: patient global impression of health; PGI-S: patient global impression of severity; PK: pharmacokinetic(s); qRT-PCR: quantitative reverse transcription polymerase chain reaction; RiiQ: Respiratory Infection Intensity and Impact Questionnaire; RSV: respiratory syncytial virus; URTI: upper respiratory tract infection

RSV LRTI will be defined as the development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough, …) AND

Positive RSV test from lower respiratory tract sample (eg, sputum, induced sputum, bronchoalveolar lavage (BAL), lung biopsy, or autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a lower respiratory tract infection; OR

Positive RSV test from lower respiratory tract sample (eg, sputum, induced sputum, BAL, lung biopsy, or autopsy specimen) only; OR

Positive RSV test from upper respiratory tract sample within ±4 days of a new chest image finding, compared to baseline, consistent with a RSV lower respiratory tract infection

as determined by the EAC.

RSV-associated LRTC will be defined as the development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough, …) AND falling within one of the following subcategories as determined by the EAC:

- RSV LRTI defined as above

OR

- Secondary bacterial LRTI defined as:

  Positive specimen for a clinically significant bacterium from lower respiratory tract source (eg, sputum, induced sputum, BAL, lung biopsy, or autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a lower respiratory tract infection

OR

- Secondary LRTI due to unusual pathogens defined as:

  Positive specimen for a clinically significant unusual organism (eg, atypical bacteria, fungus, or another respiratory virus) from a lower respiratory tract source (eg, sputum, induced sputum, BAL, lung biopsy, autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a lower respiratory tract infection

OR

- Secondary LRTC of unknown etiology defined as:

  New findings on a chest image, compared to baseline, consistent with a lower respiratory tract infection, inflammatory process, or some other clinically significant pulmonary process in absence of a positive specimen or no specimen collected from lower respiratory tract source within ±4 days of the new chest image finding

Hypothesis

The primary hypothesis of this study is that JNJ-53718678 reduces the proportion of adult HSCT recipients with RSV URTI who develop RSV LRTI within 28 days after start of treatment as compared to placebo, assessed through the relative risk.

OVERALL DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the clinical outcomes, antiviral activity, safety, tolerability, PK, and PK/PD of JNJ-53718678 in adult (ie, adult cohort) and adolescent (ie, adolescent cohort) HSCT recipients with an RSV URTI.

An interim analysis will be performed when approximately 50% of the planned participants in the adult cohort have completed the Day 28 assessments (or discontinued earlier). This interim analysis will include safety, testing for futility, early superiority, and a sample size re-estimation.

The final analysis is planned after the target number of all participants in the adult cohort has been reached and when all participants in both cohorts have completed the study (or discontinued earlier).

An Independent Data Monitoring Committee (IDMC) will be established to monitor and review data in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this study. The committee will meet periodically to review safety data and will meet to review the results from the interim analysis. After the review, the IDMC will provide recommendations to the Sponsor Committee, who will be responsible for decision making, considering the IDMC recommendation, and who will communicate these decisions to the study team.

A separate substudy with Qualitative Patient Interviews will be performed at selected study sites by a qualified person selected by the sponsor in a subset of participants to gain insight in HSCT recipients experience throughout the clinical course of their RSV infection, and to guide interpretation of treatment outcomes and study endpoints. Details, including objectives and study design, will be described in a separate substudy protocol.

The end of study is considered as the last visit (phone visit or on-site visit) for the last participant in the study.

NUMBER OF PARTICIPANTS

Participants will be enrolled in either the adult or adolescent cohort:

- Adult cohort: adult participants ≥18 to ≤75 years of age.
- Adolescent cohort: adolescent participants ≥13 to <18 years of age.

In the adult cohort, a sample size of approximately 249 participants is targeted, with a maximum of 375 participants. No target sample size was determined for the adolescent cohort.

INTERVENTION GROUPS AND DURATION

The study will include a Screening Period (Day -2 to Day 1), a Treatment Period (Day 1 to Day 21), and a Follow-up Period (Day 22 to Day 49). On Day 49, participants will complete the study. The total study duration for each participant will be approximately 49 days (Screening included).

Eligible participants will be randomized 2:1 (active:placebo) within each cohort to receive either JNJ-53718678 for 21 days or placebo for 21 days. Participants will be administered 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors), 125 mg bid for 21 days (when coadministered with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole), and 125 mg qd for 21 days (when coadministered with posaconazole) as oral suspension of JNJ-53718678, or the same volume of placebo suspension. For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be administered as eq. 125 mg oral film-coated tablets (further referred to as 125 mg oral film-coated tablets) or matching placebo (see Table below).

Study intervention administration should start as soon as possible, but no later than 4 hours after randomization and within 4 days after symptom onset of RSV URTI. Dosing should preferably occur approximately at the same time each day (for the qd dosing and for the AM and PM dosing of the bid regimen).

For participants on bid dosing, dosing should occur approximately 12 hours apart. For participants who receive the first dose of study intervention PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive bid doses in total. Administration of the second bid dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule.

Participants on a 125 mg qd regimen coadministered with posaconazole will receive 21 consecutive doses in total.

Table: Treatment Overview

Treatment	Dosing Regimen	Formulation[d]
A	250 mg JNJ-53718678[a] twice daily for 21 days without coadministration with moderate or strong CYP3A4 inhibitors	12.5 mL oral suspension[b] of JNJ-53718678 or 2 eq. 125 mg oral film-coated tablets[c]
A	125 mg JNJ-53718678[a] twice daily for 21 days if coadministration with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole	6.25 mL oral suspension of JNJ-53718678 or 1 eq. 125 mg oral film-coated tablet[c]
A	125 mg JNJ-53718678[a] once daily for 21 days if coadministration with posaconazole	6.25 mL oral suspension of JNJ-53718678 or 1 eq. 125 mg oral film-coated tablet[c]
B	Matching placebo twice daily for 21 days	12.5 mL matching placebo suspension or 2 matching oral placebo tablets
B	Matching placebo twice daily for 21 days	6.25 mL matching placebo suspension or 1 matching oral placebo tablet
B	Matching placebo once daily for 21 days	6.25 mL matching placebo suspension or 1 matching oral placebo tablet

a) Doses are provided for JNJ 53718678 AAA.
b) JNJ 53718678 is dosed as an oral suspension containing 23 mg/mL JNJ 53718678 ZCL, the hemi tartrate salt of JNJ 53718678 AAA, which is equivalent to 20 mg/mL JNJ 53718678 AAA.
c) For newly enrolled participants after implementation of Protocol Amendment 6, the drug product is administered as eq. 125 mg oral film coated tablets (containing 143.75 mg of JNJ 53718678 ZCL, the hemi tartrate of JNJ 53718678 AAA). Note that the tablet may also be dispersed in water before administration through a nasogastric tube, if applicable.
d) A participant receiving oral suspension must complete the study with the same formulation.

Study supplies will be delivered in a 2-bottle concept to be reconstituted to an oral suspension prior to dispensing to the participant. For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be supplied as oral film-coated tablets in bottles.

EFFICACY EVALUATIONS

Development of Lower Respiratory Tract Infection/Complications

During the course of the study, it is anticipated that, as part of standard of care (SOC) and strongly recommended by the sponsor, investigators should perform chest imaging and/or computed tomography (CT) scans, as well as other SOC assessments, if there is any suspicion of the occurrence of an LRTI, ie, development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough), as soon as possible. If there is any suspicion of the occurrence of an LRTI, leading to chest imaging, per local SOC a lower respiratory tract sample (eg, BAL, induced sputum, or regular sputum) should be obtained for microbiologic and virologic evaluation to determine the etiology. In addition, a bilateral mid-turbinate nasal swab sample should be collected and sent to the central lab.

An external blinded Endpoint Adjudication Committee (EAC) will review clinical data to determine whether an RSV LRTI and/or RSV-associated LRTC has developed.

During the course of the study, the following results and reports from evaluations performed per SOC will be collected and will be reviewed by an EAC:

- images and reports from chest imaging, including the reports from the central reader
- results of all local microbiology and virology tests performed (all bacterial, viral, fungal, parasite, or other results from any respiratory system-related sample [eg, BAL, sputum, pleural fluid, or lung tissue] and from blood specimens, including bacterial culture, virology (mostly by polymerase chain reaction [PCR]), and serology studies)
- ECG tracings and reports of any ECG performed in relation to a suspected LRTI event

- body temperature
- clinical notes
- autopsy reports (if applicable)
- clinical course evaluations, including the specific reason for the repeat imaging
- other supporting documents, as requested.

Clinical Course of RSV Infection

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

- respiratory rate, heart rate, SpO_2, and body temperature as measured by the investigator during scheduled visits
- respiratory signs and symptoms, including auscultation findings, as evaluated by the investigator
- requirement for supplemental O_2
- supplemental O_2 type (eg, supplemental oxygen, noninvasive pressure ventilation, endotracheal-mechanical ventilation), and duration
- (re)hospitalization by level of care during treatment and follow-up
- duration of (re)hospitalization and duration of ICU use
- respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and all-cause mortality
- Grade 3 and Grade 4 AEs in the Infections and Infestations System Organ Class
- respiratory and thoracic-related AEs
- the use of antibiotics in participants who develop RSV LRTI per the EAC's assessment and in participants who do not develop RSV LRTI
- duration and severity of RSV signs and symptoms, as assessed by the participant using the RiiQ Symptom Scale and Patient Global Impression (PGI) questions (ie, PGI of Severity [PGI-S], PGI of Health [PGI-H], and PGI of Change in Health [PGI-C])
- occurrence of GVHD or delayed engraftment as evaluated by the investigator

Antiviral Activity

For the evaluation of antiviral activity, the RSV viral load in bilateral mid-turbinate nasal swab samples will be measured at the central laboratory using an RSV qRT-PCR assay. After randomization on Day 1, but immediately predose, a bilateral mid-turbinate nasal swab sample will be collected as close as possible and prior to the first administration of study intervention, aliquoted and sent to the central lab.

During the subsequent visits, a bilateral mid-turbinate nasal swab sample will be collected, preferably at approximately the same time as the predose bilateral mid-turbinate nasal swab sample taken on Day 1 and preferably prior to dose administration, if applicable. This sample will be aliquoted and sent to the central lab.

In case of suspicion of the occurrence of an RSV LRTI, an additional bilateral mid-turbinate nasal swab sample should be collected. This sample will be aliquoted and sent to the central lab.

For a selected set of bilateral mid-turbinate nasal swab samples, quantitative RSV culture may be performed, if feasible, for determination of RSV infectious viral titer.

Health-related Quality of Life

Participants will complete the EQ-5D-5L and RiiQ Impact Scales to characterize the impact of RSV and its treatment on HRQOL.

Viral Sequencing

Development of viral resistance will be monitored by sequencing of the RSV F-gene in all baseline bilateral mid-turbinate nasal swab samples and in subsequent bilateral mid-turbinate nasal swab samples upon request of the sponsor's virologist. Other regions of the RSV genome may also be sequenced at the discretion of the sponsor's virologist.

Evaluation of RSV Viremia

In addition, blood samples for RSV detection and quantification of RSV viral load in plasma will be collected.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic assessments during the study will be based on sparse sampling for all participants and a rich serial PK sampling substudy in approximately 30 hospitalized participants at selected sites.

OTHER EVALUATIONS

Pharmacokinetics/Pharmacodynamics

The PK/PD relationship of JNJ-53718678 exposure with selected efficacy (change in viral load from baseline and clinical outcomes) and safety (including AEs and laboratory abnormalities) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships.

Biomarkers

Blood samples will be collected for exploratory biomarker analyses (host RNA and/or proteins), on the premise that these markers may play a role in the treatment response, PK, safety of JNJ-53718678, or the status and course of RSV-related disease. In addition, leftover bilateral mid-turbinate nasal swab or blood samples may be used for biomarker analysis. Analyses of biomarkers may be conducted at the sponsor's discretion and reported separately from this study. Collection of the blood samples for biomarker research is mandatory, unless local regulations require these samples to be optional.

Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected for all participants. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses.

Long-term Follow-up

Long-term follow-up data will be collected. Participants or a person designated by participants will be contacted at Day 100, Month 6, and Month 12 to collect data on survival status, morbidity (particularly complications related to RSV infection) and hospitalizations/MRU.

SAFETY EVALUATIONS

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

AEs

clinical laboratory tests (central)

ECG 12-lead

vital signs:

- vital signs assessments performed as part of the clinical course of RSV infection-related assessments (body temperature, heart rate, respiratory rate, and SpO_2)
- additional vital signs assessments: systolic blood pressure (SBP), diastolic blood pressure (DBP)

physical examination of all body systems (at Screening) (including height and body weight measurements), direct physical examination, and skin examination

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

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

Safety and tolerability will be evaluated throughout the study from signing of the ICF until the last study-related activity.

STATISTICAL METHODS

Sample Size Calculation

Sample size determination was performed for the adult cohort only. Assuming a progression to RSV LRTI occurring in 35% of the patients in the placebo arm, a relative risk of 40%, and a 2:1 randomization, 210 patients are needed to obtain 90% power with 2.5% one-sided significance in the primary analysis set based on a Fisher's Exact test. Assuming 15% of patients will be excluded from the primary analysis set, the total sample size becomes 249. Similar power estimates were obtained from simulations using Cochran-Mantel-Haenszel test and Fisher's Exact test.

Participants with an ALC <500 cells/µL at Screening should account for at least 50% of all participants in the adult cohort and participants with an ALC <200 cells/µL at Screening should account for at least 25% of all enrolled participants, also at the time of the interim analysis. To ensure the prespecified distribution in the strata for the interim analysis, enrollment in certain lymphopenia strata (≥500 - <1,000 cells/µL or 200 - <500 cells/µL) will be temporarily paused prior to the interim analysis once sufficient patients for the interim analysis are enrolled in the corresponding stratum.

To ensure the prespecified distribution in the strata for the final analysis, enrollment in certain lymphopenia strata (≥500 - <1,000 cells/µL or 200 - <500 cells/µL) could be stopped early once sufficient patients for the final analysis are enrolled in the corresponding stratum.

No target sample size was determined for the adolescent cohort.

Efficacy Analyses

For the adolescent cohort, efficacy analysis will be limited to descriptive statistics.

For the adult cohort, primary analysis of efficacy-related endpoints will be performed in the overall population, in the population with an ALC <500 cells/µL at Screening, and in the population with an ALC <200 cells/µL at Screening, applying a multiplicity correction.

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, hierarchical testing will be applied to control for overall Type I error. The following endpoints are included in the confirmatory strategy:

1. The proportion of participants who develop RSV LRTI per the EAC's assessment through Visit Day 28, ie, primary endpoint;
2. The proportion of participants who develop an RSV-associated LRTC per the EAC's assessment through Visit Day 28;
3. Time to resolution of symptoms, assessed through an instrument for patient-reported symptoms (RiiQ Symptom Scale);
4. Number of supplemental O_2 free days through Day 28;
5. Proportion of participants hospitalized (of participants who were not hospitalized at baseline);
6. The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death (all-cause mortality).
7. Total length of hospital stay (time in hospital before first dosing is discarded);

First, the primary endpoint will be tested for superiority at the 1-sided 2.5% significance level. If superiority is shown on the primary endpoint, the first secondary endpoint in the sequence as indicated above will be tested for superiority at the same significance level. If superiority is shown for this secondary endpoint, further secondary endpoints will be tested for superiority in the sequence as indicated above, and at the same significance level. In case superiority is not shown for an endpoint, no further endpoints in the sequence will be tested for superiority.

Primary Endpoint Analysis

The proportion of participants who develop an EAC-confirmed RSV LRTI through Visit Day 28 will be analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

Key Secondary Endpoint Analysis

For the hypothesis testing, the following methods will be used:

- Time to resolution of symptoms will be analyzed using a stratified Gehan-Wilcoxon test (using the randomization stratification factors).
- Total length of hospital stay and the number of supplemental O_2 free days will be analyzed using a Hodges-Lehmann test.
- For the proportion of participants hospitalized, and the proportion of participants progressing to respiratory failure and/or death, a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors, will be used as for the primary analysis.

Safety Analysis

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. The laboratory abnormalities will be determined per the criteria specified in the DMID Adult and in accordance with the normal ranges of the clinical laboratory if no gradings were available.

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

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

Electrocardiogram

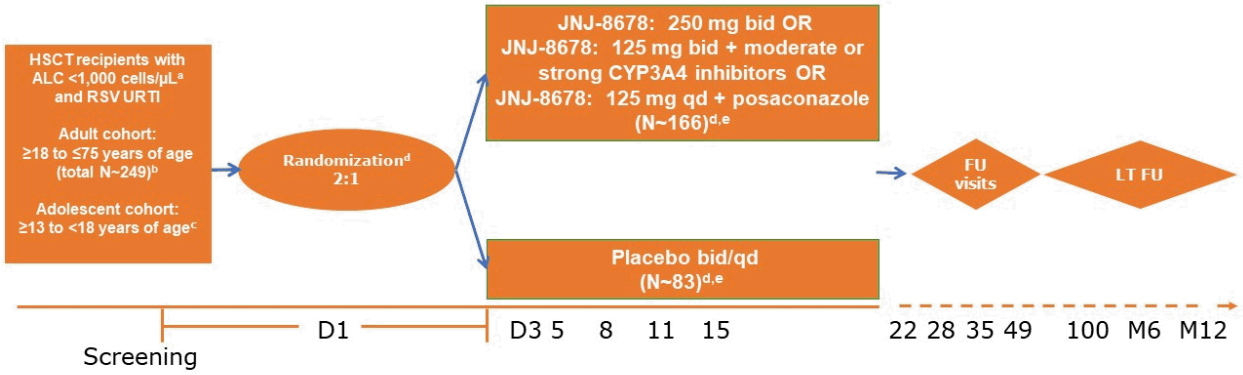
The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

Vital Signs

Descriptive statistics of and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with markedly abnormal results (specified in the SAP) will be summarized.

1.2. Schema

Figure 1: Schematic Overview of the Study



a) The local assessment confirming ALC <1,000 cells/µL should be performed no more than 48 hours prior to randomization.
b) Participants with an ALC of <500 cells/µL at the time of Screening should account for at least of 50% of all enrolled participants in the adult cohort and participants with an ALC of <200 cells/µL at the time of Screening should account for at least of 25% of all enrolled participants in the adult cohort.
c) For the adolescent cohort, no sample size was determined.
d) In the adult cohort, randomization will be stratified by hospitalization status (yes/no) at the time of randomization, lymphopenia (<200 cells/µL, 200 to <500 cells/µL and ≥500 to <1,000 cells/µL) at Screening, and ribavirin and/or intravenous immunoglobulin (IVIG) use (yes/no) at the time of randomization. No stratification will be applied to the adolescent cohort.
e) Study intervention administration should start as soon as possible, but no later than 4 hours after randomization and within 4 days after symptom onset of RSV URTI. Dosing should preferably occur approximately at the same time each day for both intakes (AM and PM), approximately 12 hours apart. For participants who receive the first dose of study intervention PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive doses in total.

1.3. Schedules of Activities

1.3.1. Hospitalization Through Discharge

Note: Once participants are discharged, they will continue their study participation per the Schedule of Activities for outpatients (see Section 1.3.2). The next scheduled visit per the outpatient SoA should be planned based on the start of dosing (Day 1), not based on the day of discharge. Overlapping assessments between both SoA on the day of discharge should be completed only once.

Phase	**Screening**	**Pre-dose**	**Treatment Phase**												**Follow-up[a]**				
Day	**-2 to 1[b]**		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**	**23-27**	**28 (±3)**	**35 (±3)**	**49 (±3) End-of-study**
Study Procedures																			
Screening/Administrative																			
Diagnostic ICF (optional)[c]	X																		
Study specific bilateral mid turbinate nasal swab for RSV diagnosis (central and local)[d,e,f]	X																		
SOC upper respiratory tract sampling and diagnostic testing using local assay[d]	X																		
Collection leftover SOC upper respiratory tract sample for central analysis	X																		
Informed Consent/Assent	X																		
Eligibility criteria[g]	X																		
Participant characteristics and demographics	X																		

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	**-2 to 1[b]**		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**	**23-27**	**28 (±3)**	**35 (±3)**	**49 (±3) End-of-study**
RSV history and characteristics	X																		
HSCT history and characteristics	X																		
Other medical history	X																		
Serum pregnancy local test[h]	X																		
Randomization	X[i]																		
Study Intervention Administration																			
Dosing study intervention[j]			bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X	bid/X					
Provision of study intervention for daily use at home at discharge[k]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)					
Confirm dosing[l]			X	X	X	X	X	X	X	X	X	X	X	X					
Efficacy Assessments																			
Clinician's evaluation of clinical course of RSV infection[m]	X	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bilateral mid turbinate nasal swab sample: RSV diagnosis confirmation, RSV viral load, presence of other viral or bacterial pathogens, viral sequencing[f,t]		X																	
Bilateral mid turbinate nasal swab sample: RSV viral load,					X		X		X		X		X		X		X	(X)[v]	

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	**-2 to 1[b]**		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**	**23-27**	**28 (±3)**	**35 (±3)**	**49 (±3) End-of-study**
viral sequencing[f]																			
Local testing for RSV detection[u]																	X		
Blood sample for RSV viremia									X				X		X				
RiiQ Symptom Scale[w]	X	X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PGI S/PGI H[w]	X	X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
RiiQ Impact Scales[w]	X	X[n]			X		X		X		X		X		X		X		
EQ 5D 5L[w]	X	X[n]			X		X		X		X		X		X		X		
PGI C[w]					X		X		X		X		X		X		X		
Check ePRO completion compliance	Continuously																		
Medical resource utilization[x]	Continuously																		
Chest imaging	X[o]		X (on suspicion of LRTI)[p]																
Lower respiratory tract sampling			X (on suspicion of LRTI)[p,q]																
Bilateral mid turbinate nasal swab sample			X (on suspicion of LRTI)[r]																
Blood sample for RSV viremia			X (on suspicion of LRTI)[r]																
Collection of medical records associated with the diagnosis of RSV LRTI[s]	X (on suspicion of LRTI)																		
Safety Assessments																			
Systolic and diastolic blood pressure[y]	X				X		X		X		X		X		X		X	X	X

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	**-2 to 1[b]**		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**	**23-27**	**28 (±3)**	**35 (±3)**	**49 (±3) End-of-study**
Physical examination (all body systems)[z]	X																		
Directed physical examination[aa]					X		X		X		X		X		X		X	X	X
Body weight[bb]	X																X		
ECG (12 lead)[cc]	X		X[dd]		X[dd]				X				X		X		X		
Urine pregnancy local test[h]																	X		
Clinical Laboratory Assessments																			
Blood sampling for hematology and biochemistry[ee]	X[ii]				X[ii]				X[ii]				X[ii]		X		X	(X)[hh]	(X)[hh]
Urinalysis[ff]	X								X				X		X		X	(X)[hh]	(X)[hh]
Biomarker Analysis																			
Blood sampling for biomarker analysis[jj]	X				X										X				
Pharmacokinetics (see Section 1.3.4.1 for sparse PK sampling schedule and Section 1.3.4.2 for rich serial PK sampling substudy)																			
Ongoing Review																			
Adverse events	Continuously																		
Concomitant medication	Continuously																		
Record IS exposures	Continuously[gg]																		

a. If a participant prematurely discontinues study intervention for any reason before the end of the Treatment Phase, the participant is recommended to remain compliant to all study-related procedures including timely completion of all efficacy assessments up to Day 49 or at least through Day 28. In case the participant withdraws consent during the treatment or follow-up phase, optional Withdrawal and Safety Follow-up Visits will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 22 and Day 28 visits, respectively, will be performed. If the reason for withdrawal from the study is full withdrawal of consent/assent, then no additional scheduled assessments are allowed.

b. Screening/predose assessments can only start after signing of the ICF, but before randomization. All Screening/predose procedures should be completed prior to the first study intervention intake.

c. Prior to signing the main consent/assent form for the study, the participant may specifically allow for the collection and testing of bilateral mid-turbinate nasal swab samples (as part of the study-specific Screening assessment) by signing the pre-Screening (diagnostic) ICF. This is not required if an upper respiratory tract sample is collected per local SOC diagnostic testing.
d. One Screening sample (from upper respiratory tract collected per local SOC testing within 24 hours prior to start of Screening or bilateral mid-turbinate nasal swab as part of the study-specific Screening assessment) will be collected for the local diagnosis of RSV infection using a rapid PCR- or other molecular-based diagnostic assay.
e. The sample will be aliquoted and 1 aliquot will be used for local diagnostic testing and the other aliquots will be sent to the central laboratory for confirmatory analysis.
f. Two mid-turbinate nasal swabs should be collected, one from each nostril, and both swabs should be put in the same universal transport medium tube (ie, a bilateral mid-turbinate nasal swab sample). Only at times when sampling of both nostrils is not feasible, such as in case of bleeding in one nostril, one mid-turbinate nasal swab should be collected from one nostril (ie, the non-bleeding nostril). Detailed information on sample collection is available in Section 8.2.3. Leftover bilateral mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at the discretion of the sponsor.
g. Investigators should ensure that all study enrollment criteria have been met at Screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study intervention is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
h. For women of childbearing potential only.
i. Randomization should occur as soon as possible after confirming eligibility (including the radiologist's or investigator's interpretation of a chest X-ray, the confirmation of ALC <1,000 cells/µL [local testing], and confirmation of RSV positivity). Randomization should preferentially occur within 24 hours after start of Screening or at the latest within 48 hours after the collection of a chest X-ray and the collection of (local) samples for confirmation of ALC <1,000 cells/µL, and for confirmation of RSV positivity. Additionally, samples for central laboratory will be collected. Randomization is to occur predose.
j. Participants will be administered 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors), 125 mg bid for 21 days (when coadministered with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole), and 125 mg qd for 21 days (when coadministered with posaconazole), or placebo. Study intervention administration should start as soon as possible, but no later than 4 hours after randomization and within 4 days after symptom onset of RSV URTI. For analysis purposes, the day of first study intervention intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day (for the qd dosing and for the AM and PM dosing of the bid regimen). For participants on bid dosing, dosing should occur approximately 12 hours apart. For participants who receive the first dose of study intervention PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive bid doses in total. Administration of the second bid dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. Participants on a 125 mg qd regimen coadministered with posaconazole will receive 21 consecutive doses in total. The study intervention can be administered with or without food. The study intervention will be administered orally. Study intervention (oral suspension or oral film-coated tablets dispersed in water) can also be administered through a nasogastric tube, if already in place
k. Study-site personnel will instruct the participants on how to use and store the study intervention for at-home dosing. At the day of discharge, sufficient study intervention will be provided to bridge the period until the next scheduled on-site visit. Suspended study intervention will be provided to participants in vials, from which the assigned volume is to be withdrawn each day. Each vial contains study intervention for 3-day dosing period. All study intervention should be stored on site and at home as instructed on the label (see Section 6.1). For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be supplied as oral film-coated tablets in bottles. Each bottle contains a sufficient number of tablets to cover study intervention for at least 7 days.
l. Date and time of the study intervention dosing needs to be recorded in the eCRF.
m. See Section 8.2.2 for an overview of assessments included in the clinical evaluation. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.
n. Only to be performed if the screening assessment occurred >8 hours before first dosing

o. A chest X-ray should be performed no more than 48 hours prior to randomization (see footnote i). If a chest X-ray has not been obtained as part of SOC, it must be obtained during Screening.
p. During the course of the study, it is anticipated as part of SOC and strongly recommended by the sponsor that investigators will perform chest imaging and/or CT scans and obtain lower respiratory tract sample (leftover to be sent to central lab; see Section 8.2.1.2), for determination of presence of RSV, if there is any suspicion of the occurrence of LRTI (see Section 8.2.1.1) as soon as possible.
q. If possible, the leftover of the local lower respiratory tract sample will be sent to the central laboratory for additional virologic analyses.
r. If the collection of a sample is planned as part of the scheduled visit, collection of an additional sample in case of suspicion of RSV LRTI is not required.
s. See Section 8.2.1.5. This will only apply to randomized participants on suspicion of LRTI.
t. A predose bilateral mid-turbinate nasal swab sample will be taken of which aliquots will be used for the central laboratory confirmation of RSV infection, to determine RSV viral load, to determine mutations in the viral genome potentially associated with resistance to JNJ-53718678, and to determine the presence of other viral or bacterial pathogens. The bilateral mid-turbinate nasal swab sample should be collected as close as possible and prior to the first administration of study intervention (on Day 1).
u. Local testing for RSV detection should be performed using a rapid PCR- or other molecular-based assay on one aliquot of the study-specific bilateral mid-turbinate nasal swab sample. A SOC upper respiratory tract sample collected at Day 28 may also be used if needed based on the local rapid PCR- or other molecular-based assay used.
v. In case of positive local test for RSV at Day 28, an additional bilateral mid-turbinate nasal swab sample will be collected at Day 35 (study site visit) for central analysis.
w. Will be collected once daily postdose (except Day 1 predose) and preferentially PM (RiiQ Symptom Scale and PGI-S/PGI-H) or at the scheduled timepoints and preferentially PM (RiiQ Impact Scales, PGI-C, and EQ-5D-5L, if applicable), in a language in which the participant is fluent, on electronic devices (eDevice). If a participant requires assistance entering responses in the eDevice, a caregiver or member of the study team who is trained can interview the participant and enter the participant's responses on the eDevice on the participant's behalf.
x. MRU will be recorded in the eCRF (see Section 8.10).
y. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
z. Physical examination of all body systems includes also height measurements and skin examination. ***Note:*** documented height (source documents) is allowed for bedridden participants.
aa. Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.
bb. Documented body weight (source documents) is allowed for bedridden participants
cc. 12-lead ECGs will be obtained for central reading. ECGs may be repeated at the discretion of the investigator. ECGs will be obtained in a supine position after 5 minutes of rest. Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period. Further, unscheduled ECG assessments/visits can be performed based on the overall clinical picture as per the investigator's clinical discretion or to confirm abnormal ECG findings.
dd. At Day1 and Day 3, ECGs should be obtained approximately 1 to 1.5 hours (fasted) or approximately 4 hours (fed) after administration of study drug. Fasted is defined as no food intake within approximately 2 hours prior to dosing and 2 hours after dosing.
ee. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Leftover blood samples may be used for exploratory biomarker analyses, at the discretion of the sponsor.
ff. Urinalysis will be performed using dipsticks provided by the central laboratory. In case of abnormalities, the urine sample will be shipped to the central laboratory for flow cytometric and/or microscopic evaluation(s).
gg. In case therapeutic drug monitoring of immunosuppressants (IS) is performed as part of SOC or per protocol instruction, the measured IS exposures are to be captured in the eCRF.
hh. Only applicable in case a participant is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at Day 28.

ii. Levels of potassium and magnesium to be determined by the local and by the central laboratory. In case of hypokalemia and/or hypomagnesemia at screening, Day 3, Day 8, or Day 15, the levels of potassium and/or magnesium should be corrected taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required. See also Section 8.4.7.2 for cardiac safety measures.

jj. Mandatory unless local regulations require these to be optional.

1.3.2. Outpatients

Note: In case outpatients are (re)hospitalized, they will continue their study participation per the Schedule of Activities for hospitalized subjects (see Section 1.3.1). The next scheduled assessments per the hospitalized SoA should be planned based on the start of dosing (Day 1), not based on the day of hospitalization. Overlapping assessments between both SoA on the day of discharge should be completed only once.

Phase	**Screening**	**Pre-dose**	**Treatment Phase**												**Follow-up**[a]				
Day	**-2 to 1**[b]		**1**	**2**	**3**[c] **(±1)**	**4**	**5**[c] **(±1)**	**6-7**	**8**[c] **(±1)**	**9-10**	**11**[c] **(±1)**	**12-14**	**15**[c] **(±1)**	**16-21**	**22**[c]	**23-27**	**28**[c] **(±3)**	**35 (±3)**	**49 (±3) End-of-study**
	Screening On-site	**Pre-dose On-site**	**Treatment On-site/**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**	**Phone follow-up/ or**[d] **on-site visit**[c]	**Phone follow-up/ or**[d] **on-site visit**[c]
Study Procedures																			
Screening/Administrative																			
Diagnostic ICF (optional)[e]	X																		
Study specific bilateral mid turbinate nasal swab for RSV diagnosis (local and central)[f,g,h,]	X																		
SOC upper respiratory tract sampling and diagnostic testing using local assay[f]	X																		
Collection leftover SOC upper respiratory tract sample for central analysis	X																		
Informed Consent/Assent	X																		
Eligibility criteria[i]	X																		

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	**-2 to 1[b]**		**1**	**2**	**3[c] (±1)**	**4**	**5[c] (±1)**	**6-7**	**8[c] (±1)**	**9-10**	**11[c] (±1)**	**12-14**	**15[c] (±1)**	**16-21**	**22[c]**	**23-27**	**28[c] (±3)**	**35 (±3)**	**49 (±3) End-of-study**
	Screening On-site	**Pre-dose On-site**	**Treatment On-site/**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**	**Phone follow-up/ or[d] on-site visit[c]**	**Phone follow-up/ or[d] on-site visit[c]**
Participant characteristics and demographics	X																		
RSV history and characteristics	X																		
HSCT history and characteristics	X																		
Other medical history	X																		
Serum pregnancy local test[j]	X																		
Randomization	X[k]																		
Study Intervention Administration																			
Dosing study intervention[l]			bid/X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X	bid/ X					
Confirm dosing[n]			X		X		X		X		X		X						
Provision of study intervention for daily use at home[m]			X				X		X		X		X						
Efficacy Assessments																			
Clinician's evaluation of clinical course of RSV infection[p]	X	X[q]	X		X		X		X		X		X		X		X	(X)[o]	(X)[o]
Bilateral mid turbinate nasal swab sample: RSV diagnosis		X																	

Phase	**Screening**	**Pre-dose**	**Treatment Phase**												**Follow-up**[a]				
Day	**-2 to 1**[b]		**1**	**2**	**3**[c] **(±1)**	**4**	**5**[c] **(±1)**	**6-7**	**8**[c] **(±1)**	**9-10**	**11**[c] **(±1)**	**12-14**	**15**[c] **(±1)**	**16-21**	**22**[c]	**23-27**	**28**[c] **(±3)**	**35 (±3)**	**49 (±3) End-of-study**
	Screening On-site	**Pre-dose On-site**	**Treatment On-site/**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**	**Phone follow-up/ or**[d] **on-site visit**[c]	**Phone follow-up/ or**[d] **on-site visit**[c]
confirmation, RSV viral load, presence of other viral or bacterial pathogens, viral sequencing[h,x]																			
Bilateral mid turbinate nasal swab sample: RSV viral load, viral sequencing[h]					X		X		X		X		X		X		X	(X)[z]	
Local testing for RSV detection[y]																	X		
Blood sample for RSV viremia									X				X		X				
RiiQ Symptom Scale[aa]	X	X[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PGI S/PGI H[aa]	X	X[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
RiiQ Impact Scales[aa]	X	X[q]			X		X		X		X		X		X		X		
EQ 5D 5L[aa]	X	X[q]			X		X		X		X		X		X		X		
PGI C[aa]					X		X		X		X		X		X		X		
Check ePRO completion compliance	Continuously																		
Medical resource utilization[bb]	Continuously																		
Chest imaging	X[r]		X (on suspicion of LRTI)[s,t]																

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	**-2 to 1[b]**		**1**	**2**	**3[c] (±1)**	**4**	**5[c] (±1)**	**6-7**	**8[c] (±1)**	**9-10**	**11[c] (±1)**	**12-14**	**15[c] (±1)**	**16-21**	**22[c]**	**23-27**	**28[c] (±3)**	**35 (±3)**	**49 (±3) End-of-study**
	Screening On-site	**Pre-dose On-site**	**Treatment On-site/**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**		**SV**	**Phone follow-up/ or[d] on-site visit[c]**	**Phone follow-up/ or[d] on-site visit[c]**
Lower respiratory tract sampling			X (on suspicion of LRTI)[s,t,u]																
Bilateral mid turbinate nasal swab sample			X (on suspicion of LRTI)[t,v]																
Blood sample for RSV viremia			X (on suspicion of LRTI)[t,v]																
Collection of medical records associated with the diagnosis of RSV LRTI[s]	X (on suspicion of LRTI)[t]																		
Safety Assessments																			
Systolic and diastolic blood pressure[cc]	X				X		X		X		X		X		X		X	(X)[o]	(X)[o]
Physical examination (all body systems)[dd]	X																		
Directed physical examination[ee]					X		X		X		X		X		X		X	(X)[o]	(X)[o]
Body weight	X																X		
ECG (12 lead)[ff]	X		X[gg]		X[gg]				X				X		X		X		
Urine pregnancy local test[j]																	X		
Clinical Laboratory Assessments																			
Blood sampling for hematology	X[kk]				X[kk]				X[kk]				X[kk]		X		X	(X)[o]	(X)[o]

Phase	Screening	Pre-dose	Treatment Phase												Follow-up[a]				
Day	-2 to 1[b]		1	2	3[c] (±1)	4	5[c] (±1)	6-7	8[c] (±1)	9-10	11[c] (±1)	12-14	15[c] (±1)	16-21	22[c]	23-27	28[c] (±3)	35 (±3)	49 (±3) End-of-study
	Screening On-site	Pre-dose On-site	Treatment On-site/		SV		SV		SV		SV		SV		SV		SV	Phone follow-up/ or[d] on-site visit[c]	Phone follow-up/ or[d] on-site visit[c]
and biochemistry[hh]																			
Urinalysis[ii]	X								X				X		X		X	(X)[o]	(X)[o]
Biomarker Analysis																			
Blood sampling for biomarker analysis[ll]	X				X										X				
Pharmacokinetics (see Section 1.3.4.1 for schedule)																			
Ongoing Review																			
Adverse events	Continuously																		
Concomitant medication	Continuously																		
Record IS exposures	Continuously[jj]																		

a. If a participant prematurely discontinues study intervention for any reason before the end of the Treatment Phase, the participant is recommended to remain compliant to all study-related procedures including timely completion of all efficacy assessments up to Day 49 or at least through Day 28In case the participant withdraws consent during the treatment or follow-up phase, optional Withdrawal and Safety Follow-up Visits will be offered. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 22 and Day 28 visits, respectively, will be performed. If the reason for withdrawal from the study is full withdrawal of consent/assent, then no additional scheduled assessments are allowed.

b. Screening/predose assessments can only start after signing of the ICF, but before randomization. All Screening/predose procedures should be completed prior to the first study intervention intake.

c. On-site visit (SV). If feasible for the study site and if allowed per local regulations, home visits are allowed instead of on-site visits (although on-site visits are preferred). Visit windows should be applied only for logistical reasons. There should be at least 1 calendar day between 2 consecutive planned on-site visits.

d. Participants will be contacted by site staff for a telephone safety follow-up visit. In case a participant is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 28 Follow-Up Visit, participants might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit at the site on Day 35 and Day 49.

e. Prior to signing the main consent/assent form for the study, the participant may specifically allow for the collection and testing of bilateral mid-turbinate nasal swab samples (as part of the study-specific Screening assessment) by signing the pre-Screening (diagnostic) ICF. This is not required if an upper respiratory tract sample is collected per local SOC testing.
f. One Screening sample (from upper respiratory tract collected per local SOC testing within 24 hours prior to start of Screening or bilateral mid-turbinate nasal swab as part of the study-specific Screening assessment) will be collected for the local diagnosis of RSV infection using a rapid PCR- or other molecular-based diagnostic assay.
g. The sample will be aliquoted and 1 aliquot will be used for local diagnostic testing and the other aliquots will be sent to the central laboratory for confirmatory analysis
h. Two mid-turbinate nasal swabs should be collected, one from each nostril, and both swabs should be put in the same universal transport medium tube (ie, a bilateral mid-turbinate nasal swab sample) and the sample will be aliquoted. Only at times when sampling of both nostrils is not feasible, such as in case of bleeding in one nostril, one mid-turbinate nasal swab should be collected from one nostril (ie, the non-bleeding nostril). Detailed information on sample collection is available in Section 8.2.3. Leftover bilateral mid-turbinate nasal swab samples may be used for exploratory biomarker analyses, at the discretion of the sponsor.
i. Investigators should ensure that all study enrollment criteria have been met at Screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study intervention is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
j. For women of childbearing potential only.
k. Randomization should occur as soon as possible after confirming eligibility (including the radiologist's or investigator's interpretation of a chest X-ray, the confirmation of ALC <1,000 cells/µL [local testing], and confirmation of RSV positivity). Randomization should preferentially occur within 24 hours after start of Screening or at the latest within 48 hours after the collection of a chest X-ray and the collection of (local) samples for confirmation of ALC <1,000 cells/µL, and for confirmation of RSV positivity. Additionally, samples for central laboratory will be collected. Randomization is to occur predose.
l. Participants will be administered 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors), 125 mg bid for 21 days (when coadministered with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole), and 125 mg qd for 21 days (when coadministered with posaconazole), or placebo. Study intervention administration should start as soon as possible, but no later than 4 hours after randomization and within 4 days after symptom onset of RSV URTI. For analysis purposes, the day of first study intervention intake will be considered Day 1. Dosing should preferably occur approximately at the same time each day (for the qd dosing and for the AM and PM dosing of the bid regimen). For participants on bid dosing, dosing should occur approximately 12 hours apart. For participants who receive the first dose of study intervention PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive bid doses in total. Administration of the second bid dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule. Participants on a 125 mg qd regimen coadministered with posaconazole will receive 21 consecutive doses in total. The study intervention can be administered with or without food. The study intervention will be administered orally.
m. Study-site personnel will instruct the participants on how to use and store the study intervention for at-home dosing. Suspended study intervention will be provided to participants in vials, from which the assigned volume is to be withdrawn each day. Each vial contains study intervention for 3-day dosing period. All study intervention should be stored on site and at home as instructed on the label (see Section 6.1). For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be supplied as oral film-coated tablets in bottles. Each bottle contains a sufficient number of tablets to cover study intervention for at least 7 days.
n. On Day 1, date and time of the study intervention dosing needs to be recorded in the eCRF. At the subsequent on-site visits, participants will be asked to confirm intake of study intervention as planned since the previous on-site visit.
o. Only applicable in case of on-site visit and to be performed at the discretion of the investigator.
p. See Section 8.2.2 for an overview of assessments included in the clinical evaluation. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.

q. Only to be performed if the screening assessment occurred >8 hours before first dosing
r. A chest X-ray should be performed no more than 48 hours prior to randomization (see footnote k). If a chest X-ray has not been obtained as part of SOC, it must be obtained during Screening.
s. During the course of the study, it is anticipated as part of SOC and strongly recommended by the sponsor that investigators will perform chest imaging and/or CT scans and obtain lower respiratory tract sample (leftover to be sent to central lab; see Section 8.2.1.2), for determination of presence of RSV, if there is any suspicion of the occurrence of LRTI (see Section 8.2.1.1), as soon as possible.
t. Outpatients must be instructed to contact the site immediately when there is a deterioration in their condition and should be invited for an unscheduled visit to be evaluated for the development of an LRTI.
u. If possible, the leftover of the local lower respiratory tract sample will be sent to the central laboratory for additional virologic analyses.
v. If the collection of a sample is planned as part of the scheduled visit, collection of an additional sample when the occurrence of LRTI is suspected is not required.
w. See Section 8.2.1.5. This will only apply to randomized participants on suspicion of LRTI.
x. A predose bilateral mid-turbinate nasal swab sample will be taken of which aliquots will be used for the central laboratory confirmation of RSV infection, to determine RSV viral load, to determine mutations in the viral genome potentially associated with resistance to JNJ-53718678, and to determine the presence of other viral or bacterial pathogens. The bilateral mid-turbinate nasal swab sample should be collected as close as possible and prior to the first administration of study intervention (on Day 1).
y. Local testing for RSV detection should be performed using a rapid PCR- or other molecular-based assay on one aliquot of the study-specific bilateral mid-turbinate nasal swab sample. A SOC upper respiratory tract sample collected at Day 28 may also be used if needed based on the local rapid PCR- or other molecular-based assay used.
z. In case of positive local test for RSV at Day 28, an additional bilateral mid-turbinate nasal swab sample will be collected at Day 35 (study site visit) for central analysis.
aa. Will be collected once daily postdose (except Day 1 predose) and preferentially PM (RiiQ Symptom Scale and PGI-S/PGI-H) or at the scheduled timepoints and preferentially PM (RiiQ Impact Scales, PGI-C, and EQ-5D-5L, if applicable), in a language in which the participant is fluent, on electronic devices (eDevice). If a participant requires assistance entering responses in the eDevice, a caregiver or member of the study team who is trained can interview the participant and enter the participant's responses on the eDevice on the participant's behalf.
bb. Study personnel will interview participants during follow-up visits or telephone follow-up to record MRU since the last study visit. Medical resource utilization will be recorded in the eCRF.
cc. Systolic and diastolic blood pressure need to be measured sitting or supine (preferably the same position at each measurement) after at least 5 minutes of rest.
dd. Physical examination of all body systems includes also height measurements and skin examination.
ee. Directed physical examination includes respiratory system, nose, ear, throat, facial, and neck lymph nodes, and skin examination.
ff. 12-lead ECGs will be obtained for central reading. ECGs may be repeated at the discretion of the investigator. ECGs will be obtained in a supine position after 5 minutes of rest. Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period. Further, unscheduled ECG assessments/visits can be performed based on the overall clinical picture as per the investigator's clinical discretion or to confirm abnormal ECG findings.
gg. At Day 1 and Day 3, ECGs should be obtained approximately 1 to 1.5 hours (fasted) or approximately 4 hours (fed) after administration of study drug. Fasted is defined as no food intake within approximately 2 hours prior to dosing and 2 hours after dosing.
hh. Samples for clinical laboratory assessments will be collected and analyzed at a central laboratory. Leftover blood samples may be used for exploratory biomarker analyses, at the discretion of the sponsor.
ii. Urinalysis will be performed using dipsticks provided by the central laboratory. In case of abnormalities, the urine sample will be shipped to the central laboratory for flow cytometric and/or microscopic evaluation(s).

jj. In case therapeutic drug monitoring of immunosuppressants (IS) is performed as part of SOC or per protocol instruction, the measured IS exposures are to be captured in the eCRF.
kk. Levels of potassium and magnesium to be determined by the local and by the central laboratory. In case of hypokalemia and/or hypomagnesemia at screening, Day 3, Day 8, or Day 15, the levels of potassium and/or magnesium should be corrected taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required. See also Section 8.4.7.2 for cardiac safety measures.
ll. Mandatory unless local regulations require these to be optional.

Note 1: Additional, unscheduled visits can be scheduled at the discretion of the investigator for work-up of suspected LRTI or follow-up of laboratory abnormalities, ECG abnormalities, (an) AE(s).
Note 2*:* See Section 10.12, Appendix 12 for guidance on study conduct during the COVID-19 pandemic.

1.3.3. Long-term Follow-up

Phase	**Long-term Follow-up**		
Timepoint[a]	**Day 100 ± 1 Week Phone follow up**[b]	**Month 6 ± 1 Week Phone follow up**[b]	**Month 12 ± 1 Week Phone follow up**[b]
Study Procedures			
Morbidity including medical events[c]	X	X	X
Medical resource utilization[d]	X	X	X
Survival status	X	X	X

a. From first dose.
b. Preferentially phone call but other appropriate means are also acceptable, eg, Skype, WhatsApp, and others, depending on site preferences and local regulations.
c. Medical events, particularly complications related to the RSV infection including respiratory complications, GVHD onset or worsening, extended engraftment period, relapse.
d. Medical resource utilization = hospitalizations as well as data on inpatient rehabilitation, long-term care hospitalization and use of extra skilled nursing (home) will be collected.

1.3.4. PK Assessments

1.3.4.1. Sparse PK Sampling and Assessments

Table 1: Sparse PK Sampling in Hospitalized Participants

Phase	Pre-dose	Treatment Phase												Follow-up
Day		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**
Blood sampling for JNJ 53718678 pharmacokinetics (sparse)[a]		X[b,c]		X[d]				X[c,d]				X[b]		X[e]

a. Venous blood samples for determination of JNJ-53718678 plasma concentrations. Detailed information on sample collection is available in Section 8. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at the discretion of the sponsor.
b. One sample approximately 1 to 1.5 hours post dose.
c. Sparse samples on Day 1 and Day 8 are not needed for the participants of the rich serial PK sampling substudy.
d. At least 4 hours after AM dosing and prior to PM dosing for bid dosing; at least 4 hours after dosing for qd dosing.
e. At random time of the day.

Table 2: Sparse PK Sampling in Outpatients

Phase	Pre-dose	Treatment Phase												Follow-up
Day		**1**	**2**	**3 (±1)**	**4**	**5 (±1)**	**6-7**	**8 (±1)**	**9-10**	**11 (±1)**	**12-14**	**15 (±1)**	**16-21**	**22**
	Pre-dose	**Treatment On-site/**		**Site Visit (SV)**		**SV**		**SV**		**SV**		**SV**		**SV**
Blood sampling for JNJ 53718678 pharmacokinetics (sparse)[a]		X[b]		X[c]				X[c]				X[b]		X[c]

a. Venous blood samples for determination of JNJ-53718678 plasma concentrations. Detailed information on sample collection is available in Section 8. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at the discretion of the sponsor.
b. One sample approximately 1 to 1.5 hours post dose.
c. At random time of the day.

1.3.4.2. Rich Serial PK Sampling Substudy Assessments

Table 3: Rich Serial PK Sampling Substudy in Hospitalized Participants (N~30)

Time of Visit	Sampling Time (hours)								
	pre-dose	dosing	0.5h	1h	1.5h	2h	4h	8h	12h or 24h
Day 1[a]	X (-0.5h)		X	X	X	X	X	X	X
Day 8[a]	X (-0.5h)		X	X	X	X	X	X	X

Venous blood samples for determination of JNJ-53718678 plasma concentrations. Detailed information on sample collection is available in Section 8. Leftover blood samples collected for other testing may be used for exploratory biomarker analyses, at the discretion of the sponsor. Sampling is preferably to be performed at the indicated sampling time, although small deviations (up to 10 minutes) are allowed.

a. Sparse samples on Day 1 and Day 8 (as outlined in Table 1) are not needed for the participants of the rich serial PK sampling substudy.

2. INTRODUCTION

JNJ-53718678 is an investigational, potent small-molecule respiratory syncytial virus (RSV)-specific fusion inhibitor belonging to the indole chemical class which targets the F-protein and prevents the conformational changes of the F-protein required for fusion of the viral envelope with the host cell membrane, thereby inhibiting viral replication and syncytia formation.

For the most comprehensive nonclinical and clinical information regarding JNJ-53718678, refer to the most recent edition of the Investigator's Brochure (IB) and Addenda for JNJ-53718678.[34]

The term “study intervention” throughout the protocol, refers to the intake of study medication.

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

2.1. Study Rationale

Respiratory syncytial virus is a negative-stranded ribonucleic acid (RNA) virus belonging to the *Pneumoviridae* family. Although RSV is generally recognized as the major respiratory pathogen in infants and young children,[25,41] it frequently causes upper and lower respiratory illness among all age groups, often going undiagnosed. However, persons with certain high-risk conditions, such as the frail elderly, patients with chronic lung or cardiac disease, and immunocompromised (IC) patients are more susceptible to severe disease.[19,22]

Immunocompromised patients (eg, hematopoietic stem cell transplant [HSCT] recipients, subjects with congenital immunodeficiency, solid organ transplant recipients, human immunodeficiency virus [HIV]-infected patients) have a reduced ability to combat infection due to an impaired or weakened immune system. Within the IC population, HSCT recipients are generally regarded as having a particularly high risk for more severe disease caused by RSV, representing a substantial unmet need for antiviral treatment of RSV infections in this patient population.[22,32] The highest risk has been observed in allogenic transplants compared to autologous transplants and in HSCT recipients with an absolute lymphocyte count (ALC) <200 cells/µL.[43,50,53]

Progression of RSV infection from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) occurs in 17% to 84% of RSV-infected patients in the HSCT population.[4,9,24,37,39,44,48,49,51] Subsequently, these LRTIs can result in significant morbidity, often leading to hospitalizations and intensive care unit (ICU) admissions for supportive care, and are a major cause of mortality in these patients.[18,52]

There are currently no direct-acting antiviral agents approved for prevention or treatment of RSV infections in HSCT recipients. In the HSCT population, despite the lack of well-designed clinical studies, aerosolized ribavirin has been highlighted as a potential treatment strategy for RSV-associated LRTI, either as monotherapy or in combination with an immunomodulator.[32,51,52] However, ribavirin has teratogenic potential and is logistically difficult to administer via aerosol.[1,6] Other therapies for RSV infection, for which even less supportive efficacy data are available, such as oral or intravenous ribavirin, intravenous immunoglobulin (IVIG), or anti-RSV-enriched

antibody preparations are used at some clinical centers. Due to the significant disease burden and the lack of effective treatment, the unmet medical need (prophylactically and therapeutically) is substantial in the RSV-infected HSCT recipient population.

Results from a recent study in HSCT recipients with the fusion inhibitor presatovir (NCT02254408)[8,45] suggest that treatment with a fusion inhibitor may reduce RSV viral load and the rate of progression from URTI to a lower respiratory tract complication (RSV-associated LRTC; see Section 3), and as such may positively affect the clinical course.

This study will therefore evaluate the clinical outcomes, antiviral activity, safety, tolerability, pharmacokinetics (PK), and PK/pharmacodynamics (PD) of JNJ-53718678 (also a fusion inhibitor) in adult and adolescent RSV-infected HSCT recipients with acute URTI symptoms.

2.2. Background

Nonclinical Studies

JNJ-53718678 has been extensively evaluated and characterized in both in vitro and in vivo pharmacological, PK, and toxicological studies. These nonclinical in vitro and animal in vivo efficacy data demonstrate that JNJ-53718678 is a selective and potent small-molecule RSV fusion inhibitor, capable of significantly reducing the viral titer in preclinical RSV models. Concurrently, a decrease of the virus-induced pro-inflammatory response was observed in RSV-infected and JNJ-53718678 treated Balb/C mice and neonatal lambs. No in vitro antiviral activity was observed for the JNJ-53718678 minor metabolites M12 (JNJ-53541683), M19 (JNJ-64564071), and M37 (JNJ-69101045), while activity was observed for M5 (JNJ-54172794) which was lower than the activity observed for JNJ-53718678. Detailed results of performed nonclinical studies are described in Section 3 of the most recent edition of the IB and any Addenda for JNJ-53718678.[34]

Clinical Studies

Detailed results of performed clinical studies are described in the most recent edition of the IB and any Addenda for JNJ-53718678.[34] During completed adult studies 53718678RSV1001, 53718678RSV1002, 53718678RSV1004, 53718678RSV1006, 53718678RSV1008, and 53718678RSV2001, a total of 190 participants were enrolled, of whom 156 received at least 1 dose of JNJ-53718678 (oral solution) as single doses up to 1,000 mg or multiple doses up to a total daily dose of 500 mg (as 500 mg once daily [qd] or 250 mg twice daily [bid]) for up to 13 days. Of those, 106 were healthy adult participants and 50 were healthy adult participants who were inoculated with RSV-A Memphis 37b virus. In Study 53718678RSV1003, 12 participants were enrolled but they were only to taste and not to swallow the oral solutions of JNJ-53718678.

Efficacy

In a challenge model for RSV infection in healthy adults (Study 53718678RSV2001), exposure to JNJ-53718678 resulted in a reduction of viral load over time in all JNJ-53718678 dose groups (75 mg, 200 mg, and 500 mg) as compared to the placebo group with no clear dose-response for the active groups. This was paralleled with lower clinical symptom scores and mucus production

for the JNJ-53718678 dosing groups as compared to the placebo group. Hence, based on these efficacy data, antiviral proof-of-concept for JNJ-53718678 has been established.

Interim analysis results of the adult Study 53718678RSV2004 demonstrated positive trends for time to first confirmed RSV undetectability and time to symptom resolution of Key RSV Symptoms for JNJ-53718678 compared to placebo. For most analyses, the treatment effects appeared greater in the subgroup of participants with onset of symptoms ≤3 days compared to the subgroup with symptom onset >3 to 5 days. In Study 53718678RSV1005 in pediatric participants, a trend towards an early antiviral effect of JNJ-53718678 was observed, despite a limited data set, particularly in the placebo arms:

- effect on viral load change from baseline on Days 2 and 3 (1 to 2 logs difference) compared to placebo;
- effect on viral load area under the curve (AUC) on Day 3 and Day 7 (20% to 25% reduction) compared to placebo.

The exploration of the effects on the clinical course of RSV infection did not reveal a difference between participants who had received JNJ-53718678 and those who had received placebo in this limited dataset. No dose-response relationship could be observed across the JNJ-53718678 dose levels.

Human Pharmacokinetics

In the single dose escalation part of Study 53718678RSV1001, the mean maximum plasma concentration (C_{max}) of JNJ-53718678 increased proportionally with dose after administration of JNJ-53718678 doses between 25 mg and 1,000 mg under fasted conditions. Mean AUC from time of administration extrapolated to infinity ($AUC_{0\ \infty}$) of JNJ-53718678 appeared to increase slightly more than dose-proportionally with increasing JNJ-53718678 dose from 25 mg to 1,000 mg. Median time to maximum plasma concentration (t_{max}) was 1.0 hour, except for the 1,000-mg dose group, which was 2.5 hours. Mean half-life ($t_{1/2term}$) ranged from 9.3 to 10.3 hours for the 75-mg dose group to the 1,000-mg dose group. Based upon data from Study 53718678RSV1004 and Study 53718678RSV1001, C_{max} and $AUC_{0\ \infty}$ for JNJ-53718678 are similar between Caucasian and Japanese participants.

In the multiple dose escalation part of Study 53718678RSV1001 under fed conditions, steady state conditions were generally reached after 1 day of treatment with JNJ-53718678. At steady state on Day 8, JNJ-53718678 exposure expressed as mean predose plasma concentration (C_{trough}), minimum plasma concentration (C_{min}), C_{max} and $AUC_{0\ 24h}$ showed a dose-proportional increase with increasing JNJ-53718678 dose from 250 mg every 24 hours (q24h) to 500 mg q24h. Mean C_{trough} and C_{min} were somewhat higher for the 250 mg every 12 hours (q12h) dose regimen compared with the 500 mg q24h dose regimen. C_{max} was lower, and average plasma concentration at steady state over the dosing interval (C_{avg}) and $AUC_{0\ 24h}$ were somewhat lower for the 250 mg q12h compared with the 500 mg q24h dose regimen. The mean 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 q12h. Mean renal clearance was very low, and similar between dose regimens.

In Study 53718678RSV2001, the multiple-dose PK results in adult participants inoculated with RSV-A Memphis 37b virus were in line with those from Study 53718678RSV1001, indicating that viral infection did not affect the PK of JNJ-53718678.

Results from the mass balance-study 53718678RSV1008 demonstrated that JNJ-53718678 was the major entity in plasma (44% to 47%), with M12 and M37 being the most abundant metabolites at 17% to 22% and approximately 10% of $AUC_{0\ 96h}$ of tissue radioactivity (TR), respectively; M19, M5, and glucuronide metabolites (M8 and M9) represented 5%, 4%, and 1% (each), respectively. Most of TR was recovered in feces (71%) and urine (20%), with unchanged drug representing 10% to 16% and 1%, respectively.

The PK results from the study part evaluating the oral suspension in Study 53718678RSV1007, indicated similar bioavailability of the oral suspension compared to the oral solution formulation, with a relative bioavailability of 109% (C_{max}) and 104% (AUC).

The 125 mg oral film-coated tablets, to be used after implementation of Protocol Amendment 6, were evaluated as "oral solid concept formulation G033" in Study 53718678RSV1011. Interim PK results in 24 healthy participants from Study 53718678RSV1011 (Part 1) demonstrated similar bioavailability of the oral solid concept formulation compared to the oral suspension formulation (provided as powder G007 + solvent G005), with a relative bioavailability (90% CI) of ~91% (83-99%) (C_{max}) and ~98% (93-103%) (AUC) under fasted conditions. The median T_{max} was 1.5 hours under fasted condition and 4 hours under fed condition for the oral film-coated tablets.

In Study 53718678RSV1009, the effect of JNJ-53718678 on the cardiac repolarization interval in healthy adult participants was evaluated with dosing up to 4,500 mg. Part 1 of the study was the dose escalation part; based on the PK and safety results of Part 1, the supratherapeutic dose of 4,500 mg was selected for Part 2 of the study, the thorough QT (TQT) part. Exposure-response analysis was performed to determine the relationship between the concentrations of JNJ-53718678 and QT/QTc interval changes extracted from Holter monitor electrocardiogram (ECG) data. Based on this analysis, an important potential risk of QT interval prolongation was identified for JNJ-53718678. The model-predicted mean placebo-corrected change from baseline for the individual-corrected QTc (ΔΔQTcI) (90% CI) at the observed geometric mean of the C_{max} of the effect compartment concentration following a single dose of 500 mg (2,165 ng/mL) and 4,500 mg (10,153 ng/mL) JNJ-53718678 was 4.8 ms (4.2; 5.3 ms) and 20.3 ms (18.2; 22.3 ms), respectively. The highest C_{max} at the effect compartment following a single dose associated with an upper limit of the 90%CI for ΔΔQTcI <10 ms was 4,350 ng/mL, which corresponds with approximately a single dose of 1,000 mg. For more details on the analysis, refer to the most recent version of the IB and any Addenda.[34]

A population PK (popPK) model for JNJ-53718678 has been developed using data from Phase 1 studies in healthy adults (Studies 53718678RSV1001, 53718678RSV1007, 53718678RSV1008, and 53718678RSV1009) and Phase 2a Study 53718678RSV2004 in RSV-infected adults.

Interim analysis results from Study 53718678RSV2004 in RSV-infected adult patients (data cut-off 23 September 2019) demonstrate that the popPK model provides an adequate description

of most of the data, however moderate variability existed with exposures greater (~25%) than expected based on healthy volunteer data. The mean (SD) Day 7 $AUC_{0\ 24h}$ and C_{trough} following administration of 500 mg JNJ-53718678 in this study (N 16) were 38,800 (16,600) ng.hr/mL and 698 (546) ng/mL, respectively, compared to 26,520 (7,520) ng.hr/mL and 334 (197) ng/mL, respectively, observed in Study 53718678RSV2001 (N 17).

Effect of Food

The effect of food on the PK of JNJ-53718678 (oral solution) was assessed following a single dose of 250 mg JNJ-53718678 in Study 53718678RSV1001. Total exposure ($AUC_{0\ \infty}$) of JNJ-53718678 was similar between fed and fasted conditions. Additionally, PK results from the study part evaluating the oral suspension in Study 53718678RSV1007, indicated that the mean C_{max} of JNJ-53718678 was 35% lower when the oral suspension was administered under fed conditions compared to fasted conditions. The mean fed/fasted ratio was 95% for $AUC_{0\ \infty}$.

Interim PK results from Study 53718678RSV1011 of the oral solid concept formulation G033 (oral film-coated tablet to be used in the current study) demonstrated similar bioavailability compared to the oral suspension formulation (G007 powder + G005 solvent), with a relative bioavailability (90% CI) of ~72% (64-82%) (C_{max}) and ~94% (88-100%) (AUC) under fed conditions. The reduction in C_{max} under fed conditions is similar between the solid concept formulation and the oral suspension (demonstrated in Parts 6 & 7 of Study 53718678RSV1007).

Therefore, JNJ-53718678 can be taken with or without food.

Drug-drug Interactions

Based on in vitro data, JNJ-53718678 is a cytochrome P450 (CYP)2B6 inducer, a substrate but not an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein up to 15 µM, and an inhibitor of organic-anion-transporting polypeptide (OATP)1A2, OATP1B1, organic anion transporter 3, organic cation transporter (OCT)1, and OCT2. In vivo clearance of JNJ-53718678 will likely not be hepatic uptake-limited or sensitive to interactions with hepatic uptake inhibitors.

To prevent graft-versus-host disease (GVHD), patients are treated with immunosuppressive drugs to suppress donor T cell function before and after stem cell infusion. Commonly used immunosuppressive drugs include tacrolimus, sirolimus, and cyclosporine, which are known CYP3A4 substrates. The potential effect of JNJ-53718678 on the PK of sensitive CYP substrates was evaluated in the drug-drug interaction Study 53718678RSV1002.[12] In this study, the drug interaction potential of JNJ-53718678 was evaluated at a dose level of 500 mg on a drug cocktail containing selective CYP probes (CYP3A4 [midazolam], CYP1A2 [caffeine], CYP2C9 [warfarin]), and a non-selective P-gp substrate (fexofenadine). In this study, participants received JNJ-53718678 500 mg qd for a total of 13 consecutive days. Results of this study suggested a weak inhibition of CYP3A4 activity in the presence of a single dose of JNJ-53718678 and a weak induction of CYP3A4 activity after repeated administration of JNJ-53718678. Overall, at steady-state of JNJ-53718678, the exposure of midazolam is hardly affected by JNJ-53718678 due to the combined CYP3A4 inhibitory and inductive effect described. Similar effects as for midazolam are anticipated for sirolimus and tacrolimus, which are also listed as sensitive CYP3A4

substrates,[21] and for cyclosporine, which is primarily metabolized through CYP3A4. Coadministration of JNJ-53718678 with one of these immunosuppressants may initially (first dose) increase the exposure of the CYP3A4 substrate, but the exposure of the CYP3A4 substrate will subsequently gradually decrease and return to baseline due to the compensatory inductive effect. For most CYP3A4 substrates a less than 2-fold increase in exposure would not have a clinically relevant effect in terms of efficacy or safety. However, a small temporary increase in exposure of drugs having a narrow therapeutic index (such as tacrolimus and cyclosporine), may be clinically relevant. Therefore, therapeutic drug monitoring (see Section 6.6) is recommended to assure adequate immunosuppressant exposures and to allow for immunosuppressant dose adjustments. On the other hand, strong inhibitors or inducers of CYP3A4 enzymes, are not permitted as concomitant medication in the JNJ-53718678 studies (see Section 6.6).

In Study 53718678RSV1002, JNJ-53718678 had no clinically significant effect on CYP2C9 and CYP1A2. Single and multiple doses of JNJ-53718678 reduced the plasma exposure of fexofenadine. The observed decrease in exposure of fexofenadine after coadministration of a single dose of JNJ-53718678 is due to the inhibition of OATP1A2, an uptake transporter located in the gut; further reduction of the fexofenadine exposure after repeated dosing of JNJ-53718678, was likely due to induction of P-gp.

In clinical Study 53718678RSV1006, JNJ-53718678 was coadministered with itraconazole (a strong CYP3A4 and P-gp inhibitor) and with rifampicin (an inducer of CYP3A4, UGT, and P-gp, and an inhibitor of OATP). $AUC_{0\infty}$ of JNJ-53718678 increased approximately 3-fold upon coadministration with itraconazole 200 mg qd. After coadministration of JNJ-53718678 with a single dose of rifampicin, no significant change in the total exposure of JNJ-53718678 was observed, suggesting the OATP transporter is not involved in the disposition of JNJ-53718678. However, repeated administration of rifampicin 600 mg qd decreased the exposure of JNJ-53718678, primarily due to induction of CYP3A4.

Safety

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

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

who received placebo. Diarrhea, nausea, and headache were more frequently observed in participants who received JNJ-53718678 compared to participants who received placebo.

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

- One participant was reported with prolonged QT interval corrected using Fridericia's formula (QTcF) (>450 to ≤480 ms), based on findings from the safety ECG, during JNJ-53718678 (4,500 mg) treatment period, which was considered moderate in severity and probably related to the study agent. The AE resolved the same day.
- One participant was reported with the AEs vomiting, nausea, and headache during the 4,500 mg JNJ-53718678 treatment period. The AEs vomiting and nausea were considered mild in severity and possibly related to the study agent. The AE headache was considered mild in severity and doubtfully related to the study agent. A second event of vomiting was reported on the same day and was considered moderate in severity and possibly related to the study agent. These AEs resolved the same day.
- One participant was reported with a skin reaction during the 400 mg moxifloxacin treatment period. This AE was considered mild in severity and possibly related to the study agent. The AE resolved the same day.

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

Based on exposure-response analysis, an important potential risk of QT interval prolongation was identified for JNJ-53718678 (see above). For more details on the analysis, refer to the most recent version of the IB and any Addenda.[34] A change to a bid dosing regimen (see Section 4.3.1) and several other mitigation measures to safeguard the participants (see Section 2.3.3) have been implemented.

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

- Two participants (4,500 mg JNJ-53718678 and placebo) had an abnormal QTcF value between 450 and 480 ms, leading to early study discontinuation for 1 participant due to AE.
- Six participants had an abnormal QTcF change from baseline between 30 and 60 ms (2 [8.0%] after receiving 4,500 mg JNJ-53718678, 1 [4.3%] after receiving placebo, and 3 [12.5%] after

receiving 400 mg moxifloxacin) but the values remained within normal range. None of the participants had an abnormal QTcF change from baseline >60 ms.

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

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

Interim analysis of Study 53718678RSV2002 in pediatric participants (N 155) confirmed the previously established safety profile of JNJ-53718678. No changes from baseline in QTcF or QT interval corrected for heart rate according to Bazett's formula (QTcB) of >60 ms were reported.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-53718678 may be found in the most recent edition of the IB and any Addenda.[34]

2.3.1. Risks for Study Participation

2.3.1.1. Known Risks

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

2.3.1.2. Potential Risks

All therapies have the potential to cause adverse experiences. For an overview of the total number of adult participants (completed studies) receiving one or more doses of JNJ-53718678, refer to Section 2.2.

Please refer to Section 2.2 and the most recent edition of the IB and any Addenda for details on the reported AEs and laboratory/ECG abnormalities in the studies conducted to date.[34]

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

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

The evaluation of JNJ-53718678 antiviral activity requires nasal swabbing. This is a minimally invasive assessment that at most results in some short-term discomfort for the participant and is usually well tolerated, though occasionally nose bleeding can occur. Study procedures such as blood sampling carry a potential risk (eg, pain, discomfort, hematoma) to the participant.

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

Although currently no clinical data from a 21-day treatment with JNJ-53718678 are available, the treatment duration of 21 days is considered to be safe. In Study 53718678RSV1002,[12] the only study in which a dosing duration of 13 days was evaluated, steady state conditions were generally achieved at 8 days of dosing. This 13-day dosing regimen (500 mg qd) was generally safe and well tolerated (see also Section 4.3).

Lower respiratory tract samples will be obtained as per local standard of care (SOC) (including by bronchoscopy or inducing sputum) and do not expose the participant to additional risk above that from SOC.

Imaging procedures performed as part of screening, as well as part of identification of suspected LRTI, carry a risk related to the radiation exposure associated with the assessment. However, these assessments would be performed as part of SOC. The additional radiation exposure from the screening chest X-ray, if not performed as SOC, is limited.

Review of data of the TQT Study 53718678RSV1009, has identified a new important potential risk of QT prolongation for JNJ-53718678 (see Section 2.2 and the most recent version of the IB and any Addenda[34] for more information).

Overall, the oral suspension formulation used in Part 1 and 2 of the TQT study was generally safe and well tolerated in healthy adult participants. Most AEs were mild, with diarrhea being the most frequently reported AE. No Grade 3 or 4 AEs were reported during this study. From a clinical safety perspective, no clinically relevant ECG abnormalities (related to QTcF or other) or cardiovascular AEs were observed in this study. However, exposure-response analysis based on time-matched QTc Holter data demonstrated that, following a single dose of 500 mg, the effect of JNJ-53718678 on cardiac repolarization is not of regulatory concern, but at doses ≥1,000 mg an increase of ΔΔQTcI above the threshold of 10 ms can be expected (Section 2.2).

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

The safety profile of the oral film-coated tablet is similar to that of the oral suspension (Study 53718678RSV1011; data on file).

2.3.2. Benefits for Study Participation

2.3.2.1. 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, despite a limited data set (in particular the small placebo group), a trend towards an early antiviral effect of JNJ-53718678 was observed for viral load change from baseline and for viral load AUC in the pediatric population based on data from Study 53718678RSV1005 (Section 2.2).

In the ongoing adult Study 53718678RSV2004, the interim analysis (N 67) data demonstrated positive trends for time to first confirmed RSV undetectability for JNJ-53718678 compared to placebo. Effects appeared greater in the subgroup of participants with symptom onset ≤3 days compared to the subgroup with symptom onset >3 to 5 days.

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

2.3.2.2. Potential Benefits

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

In the ongoing adult Study 53718678RSV2004, the interim analysis (N 67) data demonstrated a positive trend for time to symptom resolution of Key RSV Symptoms for JNJ-53718678 compared to placebo. Effects appeared greater in the subgroup of participants with symptom onset ≤3 days compared to the subgroup with symptom onset >3 to 5 days.

2.3.3. Benefit-Risk Assessment for Study Participation

Currently the only available treatment for RSV in HSCT recipients is supportive and symptomatic care, as well as ribavirin and/or IVIG (see Section 2.2).

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 antiviral effect was established in adult healthy volunteers challenged with a laboratory strain of RSV (Study 53718678RSV2001) as well as in naturally RSV-infected pediatric participants (Study 53718678RSV1005) (Section 2.2);
- Antiviral effect proof-of-concept was established in non-hospitalized adult participants infected with RSV (interim analysis of Study 53718678RSV2004).
- No safety concerns were identified in the interim analysis of Study 53718678RSV2004 in non-hospitalized adult participants infected with RSV.
- No safety concerns were identified in studies in RSV infected pediatric participants (Study 53718678RSV1005 in children >1 month to ≤24 months of age and from an interim analysis of Study 53718678RSV2002 in children ≥28 days and ≤3 years of age) (Section 2.2).
- No safety concerns were identified in completed studies in adult healthy volunteers to date and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to JNJ-53718678 by the investigator (Section 2.2).
- Several safety measures have been proposed to minimize potential risk to participants, including:

  Only participants who meet all eligibility criteria (as specified in the protocol, Sections 5.1 and 5.2) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of the participants in the study.

  Safety data on the total daily dose selected for the current study did not identify any safety concern (see Section 4.3).

  Utilization of study intervention discontinuation criteria (see Section 7.1) and study discontinuation criteria (see Section 7.2).

  Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development (see Section 8.3) and safety topic of special interest of JNJ-53718678 as part of the study assessments (see Section 8.4.7).

  Possibility to use the results from diagnostic testing (swab) performed as part of SOC.

  The establishment of an Independent Data Monitoring Committee (IDMC) (see Section 9.5) to monitor data on a regular basis to ensure continuing safety of the participants enrolled in this study (see Sections 8.3 and 8.4).

  Additionally, given the longer dosing duration of JNJ-53718678 used in this study (see Section 4.2) and the population targeted, the IDMC will perform the first unblinded safety review prior to (should a safety signal warrant) or after the 18th patient has completed the Day 21 (end-of-intervention) assessments (or discontinued earlier).

  In view of the identified important potential risk of QT interval prolongation (see Section 2.3.1.2, TQT Study 53718678RSV1009), the following measures have been implemented to minimize the potential risk to participants:

  - The selection of the bid dose regimens which, relative to the respective qd dose regimens for which no safety concern was identified, will minimize C_{max} while still maintaining AUC and increasing C_{trough} (see Section 4.3.1).

- Dose adjustment to 250 mg bid dose for all participants without coadministration with moderate or strong CYP3A4 inhibitors. For participants coadministered with moderate or strong CYP3A4 inhibitors with the exception of posaconazole, the dose will be reduced to 125 mg bid. For participants coadministered with posaconazole, the dose will be reduced to 125 mg qd (see Sections 4.3.1, 6.1, 6.5, and 6.6).
- Specific cardiovascular and ECG-based criteria have been established for eligibility assessment (see Section 5.2).
- Close monitoring of the use of concomitant medications will be conducted regularly.
- Enhanced ECG monitoring (including around t_{max} on Day 1 and Day 3 [steady state]) will be conducted during the regular onsite visits in the treatment period (ie, at Day 1, Day 3, Day 8, and Day 15). Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period. Further, unscheduled ECG assessments/visits can be performed based on the overall clinical picture as per the investigator's clinical discretion (see Schedules of Activities and Section 8.4.7.2).
- Utilization of study intervention discontinuation and withdrawal criteria specific to QTcF interval changes (see Section 7.1).
- Close monitoring of hypokalemia and hypomagnesemia and corrective actions in case of laboratory abnormalities for these analytes at Screening and during the treatment period (see Section 8.4.7.2).
- Specific toxicity management for confirmed QTcF interval value ≥500 ms (see Section 8.4.7.2).
- Close follow-up of ECG- and cardiac-related AEs as part of medical monitoring.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with JNJ-53718678 are justified by the anticipated benefits that may be afforded to adult RSV-infected HSCT recipients with acute URTI symptoms.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the effect of JNJ-53718678 on the development of RSV LRTIs in adult HSCT recipients with RSV URTI.	The proportion of participants who develop RSV LRTI (see definition below) per the Endpoint Adjudication Committee (EAC)'s assessment (see Section 9.6) through Visit Day 28.
Secondary	
To evaluate the effect of JNJ-53718678 on the development of RSV-associated LRTC in adult and adolescent HSCT recipients with RSV URTI.	The proportion of participants who develop RSV-associated LRTC (see definition below) per the EAC's assessment (see Section 9.6) through Visit Day 28.
To evaluate the safety and tolerability of JNJ-53718678	Safety and tolerability, as assessed by AEs, clinical laboratory testing, ECGs, vital signs, throughout the study

Objectives	Endpoints
To evaluate the impact of JNJ-53718678 on progression to respiratory failure and on all-cause mortality	• The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death, in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment; • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death (all-cause mortality); • The proportion of participants progressing to death (all-cause mortality), in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment; • The proportion of participants progressing to death (all-cause mortality); • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive), in participants who develop RSV LRTI or RSV-associated LRTC per the EAC's assessment; • The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive).
To evaluate the impact of JNJ-53718678 on the clinical course of RSV infection	Clinical course-related endpoints: • Number of supplemental O_2 free days through Day 28 (see Attachment 10.8 for assessments) • Incidence of O_2 requirement, total length and type (eg, supplemental oxygen, noninvasive pressure ventilation, invasive mechanical ventilation [tracheal tube, laryngeal mask, or tracheostomy]) • Respiratory rate, heart rate, body temperature, and peripheral capillary oxygen saturation (SpO_2) over time as measured by the investigator during scheduled visits • Proportion of participants hospitalized (of participants who were not hospitalized at baseline), proportion of participants re-hospitalized (of participants who were hospitalized at baseline and discharged during the study and of participants who were not

Objectives	Endpoints
	hospitalized at baseline, required hospitalization, and were discharged during the study) • Total length of hospital stay (time in hospital before first dosing is discarded) and total time in the ICU (time in ICU before first dosing is discarded) • Incidence of Grade 3 and Grade 4 adverse events (AEs) in the Infections and Infestations System Organ Class • Incidence of respiratory and thoracic-related AEs • Incidence of antibiotic use in participants who develop and in those who do not develop RSV LRTI or RSV-associated LRTC per the EAC's assessment • Time to resolution of symptoms, assessed through an instrument for patient-reported symptoms (Respiratory Infection Intensity and Impact Questionnaire [RiiQ] Symptom Scale [Appendix 10.9]) • Change from baseline through Day 28 in severity of symptoms reported by subjects in the RiiQ Symptom Scale (Appendix 10.9) • Time to resolution of respiratory illness, through the Patient Global Impression of Severity (PGI-S) Scale (Appendix 10.10) • Change in PGI-H and PGI-C Scales through Day 28 (Appendix 10.10)
To evaluate the PK of JNJ-53718678	PK parameters of JNJ-53718678
To evaluate the relationship between the PK of JNJ-53718678 and the PD (selected antiviral activity, clinical outcomes, and safety parameters) after repeated dosing of JNJ-53718678	PK/PD analysis of plasma concentration-time data of JNJ-53718678 using (non)-linear mixed-effects modeling
To evaluate the antiviral effect of JNJ-53718678 as measured by RSV viral load in bilateral mid-turbinate nasal swab samples by quantitative reverse transcription polymerase chain reaction (qRT-PCR) assay	Virologic parameters derived from the RSV viral load as measured by a qRT-PCR assay in bilateral mid-turbinate nasal swab samples including: • RSV viral load and change from baseline over time • RSV viral load AUC from immediately prior to first dose of study intervention (baseline) through Day 8, Day 11, Day 15, Day 22, and Day 28.

Objectives	Endpoints
	• time to undetectable RSV viral load • proportion of participants with undetectable RSV viral load at each time point throughout the study
To evaluate the impact of RSV and its treatment on health-related quality of life (HRQOL).	Change from baseline for the HRQOL through Day 28 (as assessed through the 5-level EuroQol 5-Dimension [EQ-5D-5L; Appendix 10.11] and RiiQ Impact Scales (Appendix 10.9)]
To evaluate the emergence of mutations in the viral genome potentially associated with resistance to JNJ-53718678	Changes from baseline in the RSV F-gene sequence (and potentially other regions of the RSV genome, at the discretion of the sponsor's virologist)
Exploratory	
The exploratory objectives are to evaluate: • medical resource utilization (MRU), including hospitalization, for clinical management of participants during treatment and posttreatment follow-up • the RSV infectious virus titer as assessed by quantitative culture of RSV (plaque assay) on selected nasal swab samples (optional objective, pending feasibility of performing such an assay) • the relationship between antiviral activity and clinical course • the impact of the baseline RSV viral subtype and genotype on the antiviral activity and clinical course • the incidence of RSV viremia • the incidence of GVHD or graft failure	The exploratory endpoints are: • medical resource utilization • RSV viral subtype and presence of pretreatment RSV F-gene polymorphisms • virologic parameters derived from the RSV viral load as measured by quantitative viral culture • proportion of participants with RSV viremia (RSV viral load in plasma) • proportion of participants with new onset GVHD • proportion of participants with graft failure

EAC: Endpoint Adjudication Committee; ECG: electrocardiogram; EQ-5D-5L: 5-level EuroQol 5-Dimension; GVDH: graft-versus-host disease; HRQOL: health-related quality of life; LRTC: lower respiratory tract complication(s); LRTI: lower respiratory tract infection; MRU: medical resource utilization; PD: pharmacodynamic(s); PGI-C: patient global impression of change; PGI-H: patient global impression of health; PGI-S: patient global impression of severity; PK: pharmacokinetic(s); qRT-PCR: quantitative reverse transcription polymerase chain reaction; RiiQ: Respiratory Infection Intensity and Impact Questionnaire; RSV: respiratory syncytial virus; URTI: upper respiratory tract infection

RSV LRTI will be defined as the development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough) AND

Positive RSV test from lower respiratory tract sample (eg, sputum, induced sputum, bronchoalveolar lavage (BAL), lung biopsy, or autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a LRTI; OR

Positive RSV test from lower respiratory tract sample (eg, sputum, induced sputum, BAL, lung biopsy, or autopsy specimen) only; OR

Positive RSV test from upper respiratory tract sample within ±4 days of a new chest image finding, compared to baseline, consistent with a RSV LRTI

as determined by the EAC.

RSV-associated LRTC will be defined as the development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough) AND falling within one of the following subcategories as determined by the EAC:

- RSV LRTI, as defined as above

OR

- Secondary bacterial LRTI defined as:

  Positive specimen for a clinically significant bacterium from lower respiratory tract source (eg, sputum, induced sputum, BAL, lung biopsy, or autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a LRTI

OR

- Secondary LRTI due to unusual pathogens defined as:

  Positive specimen for a clinically significant unusual organism (eg, atypical bacteria, fungus, or another respiratory virus) from a lower respiratory tract source (eg, sputum, induced sputum, BAL, lung biopsy, autopsy specimen) within ±4 days of a new chest image finding, compared to baseline, consistent with a LRTI

OR

- Secondary LRTC of unknown etiology defined as:

  New findings on a chest image, compared to baseline, consistent with a LRTI, inflammatory process, or some other clinically significant pulmonary process in absence of a positive specimen or no specimen collected from lower respiratory tract source within ±4 days of the new chest image finding

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

3.1. Hypothesis

The primary hypothesis of this study is that JNJ-53718678 reduces the proportion of adult HSCT recipients with RSV URTI, who develop RSV LRTI within 28 days after start of treatment as compared to placebo, assessed through the relative risk.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the clinical outcomes, antiviral activity, safety, tolerability, PK, and PK/PD of JNJ-53718678 in adult (ie, adult cohort) and adolescent (ie, adolescent cohort) HSCT recipients with an RSV URTI.

Participants will be enrolled in either the adult or adolescent cohort:

- Adult cohort: adult participants ≥18 to ≤75 years of age.
- Adolescent cohort: adolescent participants ≥13 to <18 years of age.

In the adult cohort, a sample size of approximately 249 participants is targeted, with a maximum of 375 participants (see Section 9.4.10). No target sample size was determined for the adolescent cohort (see Section 4.2.1).

The study will include a Screening Period (Day -2 to Day 1), a Treatment Period (Day 1 to Day 21), and a Follow-up Period (Day 22 to Day 49). On Day 49, participants will complete the study. The total study duration for each participant will be approximately 49 days (Screening included).

Study participants will be identified when they present for medical care (outpatient or hospital) with new symptoms of an RSV URTI and/or worsening of chronic (associated with previously existing diagnosis, eg, chronic rhinorrhea, seasonal allergies, chronic lung disease) respiratory symptoms consistent with RSV infection. Participants will need to complete Screening and initiate study intervention dosing within 4 days after symptom onset of RSV URTI (ie, onset of new symptoms of an RSV URTI and/or worsening of chronic respiratory symptoms, consistent with RSV URTI).

During Screening, baseline HSCT-related and RSV-related characteristics will be verified. Participants need to have ALC <1,000 cells/µL at Screening to be eligible. One Screening sample (from upper respiratory tract collected per local SOC testing within 24 hours prior to start of Screening or a bilateral mid-turbinate nasal swab as part of the study-specific Screening assessment) will be collected for the local diagnosis of RSV infection using a rapid PCR- or other molecular-based diagnostic assay. A separate bilateral mid-turbinate nasal swab will be collected immediately prior to the first dose for central laboratory analyses to confirm RSV infection (and subtype), to determine the RSV viral load, to perform viral sequencing, and to determine the presence of other viral or bacterial pathogens. A chest X-ray is required for screening purposes to exclude the presence of an LRTI.

Randomization should occur as soon as possible after confirming eligibility (including the radiologist's or investigator's interpretation of a chest X-ray, the confirmation of ALC <1,000 cells/µL [local testing], and confirmation of RSV positivity). Randomization should preferentially occur within 24 hours after start of Screening or at the latest within 48 hours after the collection of a chest X-ray and the collection of (local) samples for confirmation of ALC

<1,000 cells/µL, and for confirmation of RSV positivity. Eligible participants will be randomized 2:1 (active: placebo) within each cohort to receive either:

- 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors)
- matching placebo bid for 21 days

OR

- 125 mg JNJ-53718678 bid for 21 days for participants coadministered with moderate or strong CYP3A4 inhibitors with the exception of posaconazole
- matching placebo bid for 21 days

OR

- 125 mg JNJ-53718678 qd for 21 days for participants coadministered with posaconazole
- matching placebo qd for 21 days

See also Sections 4.3.1, 6.1, 6.5, and 6.6.

Randomization in the adult cohort will be stratified by hospitalization status (yes/no) at the time of randomization, lymphopenia (<200 cells/µL, 200 - <500 cells/µL, and ≥500 - <1,000 cells/µL) at Screening, and ribavirin and/or IVIG use (yes/no) at the time of randomization. No stratification will be applied to the adolescent cohort.

Participants with an ALC <500 cells/µL at Screening should account for at least 50% of all enrolled participants in the adult cohort and participants with an ALC <200 cells/µL at Screening should account for at least 25% of all enrolled participants in the adult cohort, also at the time of the interim analysis (see Section 9.4.10).

Study intervention administration should start as soon as possible, but no later than 4 hours after randomization and within 4 days after symptom onset of RSV URTI. Dosing should preferably occur approximately at the same time each day (for the qd dosing and for the AM and PM dosing of the bid regimen).

For participants on bid dosing, dosing should occur approximately 12 hours apart. For participants who receive the first dose of JNJ-53718678 or placebo PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive bid doses in total. Administration of the second bid dose may be delayed or brought forward (by maximum 4 hours) only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule.

Participants on a 125 mg qd regimen coadministered with posaconazole will receive 21 consecutive doses in total.

JNJ-53718678/placebo can be administered with or without food. The study intervention will be administered orally. During hospitalization, the study intervention (oral suspension or oral film-coated tablets dispersed in water) can also be administered through a nasogastric tube, if already in place. In this document, both administration methods are referred to as "oral dosing", unless specified otherwise. The first dose of study intervention will be administered at the study site. During (re)hospitalization, study intervention will be administered by the study-site personnel. At home, or when the rehospitalization occurs at a non-study site, study intervention will be administered by the participant or the caregiver. All participants will receive supportive care for RSV infection as per local SOC, considering the restrictions provided in Section 6.6.

All scheduled study visits are preferentially done at the site, but can also be done as home visits, if feasible for the study site and if allowed per local regulations (both options are further referred to as 'visit'). On Day 35 and Day 49, participants will be contacted by the site staff for a telephone follow-up visit, after which the participant completes the study. In case a participant is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 28 Follow-Up Visit, participants might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit, at Day 35 and Day 49. In case a participant tests positive (locally) for RSV in a mid-turbinate nasal swab sample or other upper respiratory tract sample at Day 28, (s)he will be requested to have a site visit at Day 35 for virologic assessment.

If a participant prematurely discontinues study intervention for any reason before the end of the Treatment Phase, the participant is recommended to remain compliant to all study-related procedures including timely completion of all efficacy assessments up to Day 49 or at least through Day 28 (see Section 7.1). In case the participant withdraws consent/assent during the treatment or Follow-up phase, optional Withdrawal and Safety Follow-up Visits will be offered (see Section 7.2). If the reason for withdrawal from the study is full withdrawal of consent/assent, then no scheduled (as per Schedules of Activities) additional assessments are allowed.

During the study, the development of RSV LRTIs will be monitored (see Section 8.2.1) and the clinical course of RSV infection will be assessed (see Section 8.2.2). If there is any clinical suspicion of the occurrence of an LRTI, ie, development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough), a bilateral mid-turbinate nasal swab should be collected for central analysis and it is anticipated as part of SOC and strongly recommended by the sponsor that investigators should perform chest X-rays and/or computed tomography (CT) scans as part of the evaluation (see Section 8.2.1.1) and obtain lower respiratory tract sample consistent with local SOC (leftover to be sent to central lab) to determine the etiology. A blinded Endpoint Adjudication Committee (EAC) will review clinical data to determine whether an RSV LRTI and/or RSV-associated LRTC has developed (see Section 9.6).

For the evaluation of antiviral activity, the RSV viral load in bilateral mid-turbinate nasal swab samples will be measured at the central laboratory using an RSV qRT-PCR assay. Bilateral mid-turbinate nasal swab samples will be collected at several timepoints during the study as

indicated in the Schedules of Activities and on clinical suspicion of RSV LRTI (see Section 8.2.3). For a selected set of mid-turbinate nasal swab samples, quantitative RSV culture may be performed, if feasible, for determination of RSV infectious viral titer.

Viral resistance will be monitored by sequencing of the F-gene in all baseline bilateral mid-turbinate nasal swab samples, and on subsequent bilateral mid-turbinate nasal swab samples upon request of the sponsor's protocol virologist. Other regions of the RSV genome may also be sequenced at the discretion of the sponsor's virologist. Sequencing data will not be reported to the investigators (see Section 8.2.5). Sequencing results may be presented in a separate report.

A blood sample for evaluation of RSV viremia will be collected at several timepoints during the study as indicated in the Schedules of Activities and at clinical suspicion of LRTI. At the discretion of the sponsor, leftover from these samples may be used for an exploratory analysis of other pathogens in blood (see Section 8.2.6).

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and physical examination will be assessed throughout the study from signing of the informed consent form (ICF) until the participant's last study-related activity (see Section 8.3).

Pharmacokinetic assessments during the study will be based on sparse sampling for all participants and a rich serial PK sampling substudy in approximately 30 hospitalized participants at selected sites (see Section 8.6).

Medical resource utilization (see Section 8.10) will be assessed.

A blood sample will be collected for exploratory biomarker analyses at several timepoints during the study, as indicated in the Schedules of Activities. Leftover bilateral mid-turbinate nasal swab and blood samples obtained for other testing may also be used for exploratory biomarker analysis, at the discretion of the sponsor (see Section 8.9).

Long-term follow-up data will be collected. Participants, or a person designated by the participant, will be contacted at Day 100, Month 6, and Month 12 to collect data on survival status, morbidity (particularly complications related to the RSV infection, including respiratory complications, GVHD onset or worsening, extended engraftment period, relapse), and hospitalizations/MRU.

See Section 10.12, Appendix 12 for guidance on study conduct during the COVID-19 pandemic.

An IDMC will be established to monitor and review data in an unblinded manner on a regular basis to ensure the continuing safety of the participants enrolled in this study. The committee will meet periodically to review safety data and will meet to review the results from the interim analysis. After the review, the IDMC will provide recommendations to the Sponsor Committee, who will be responsible for decision making, considering the IDMC recommendation, and who will communicate these decisions to the study team. Details are provided in the IDMC Charter (see Section 9.5). Additionally, given the longer dosing duration of JNJ-53718678 used in this study and the population targeted, the IDMC will perform the first unblinded safety review prior

to (should a safety signal warrant) or after the 18th patient has completed the Day 28 assessments (or discontinued earlier).

An interim analysis will be performed when approximately 50% of the planned participants in the adult cohort have completed the Day 28 assessments (or discontinued earlier). This interim analysis will include safety, testing for futility, early superiority, and a sample size re-estimation (see Section 9.4.10) and will be reviewed by the IDMC.

The final analysis is planned after the target number of all participants in the adult cohort has been reached and when all participants in both cohorts have completed the study (or discontinued earlier).

A separate substudy with Qualitative Patient Interviews will be performed at selected study sites by a qualified person selected by the sponsor in a subset of participants to gain insight in HSCT recipients experience throughout the clinical course of their RSV infection, and to guide interpretation of treatment outcomes and study endpoints. Details, including objectives and study design, will be described in a separate substudy protocol.

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

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

Immunocompromised patients have a reduced ability to combat RSV infection due to an impaired or weakened immune system, and are therefore more susceptible to severe infections (see also Section 2.1). Within the IC population, HSCT recipients are generally regarded as having a particularly high risk for more severe disease caused by RSV, compared to other IC patients.[22,32] Respiratory syncytial virus infection in HSCT recipients, if left untreated, may progress quickly from RSV URTI to LRTI, which substantially impacts daily functioning.[52,56] In these patients, RSV has been recognized as one of the leading causes of morbidity and mortality, resulting in a prolonged length of hospitalization, increased rate of ICU admission, poorer overall outcomes, and reported mortality rates of 17% to 20% on average, although highly variable.[2,56] Given the absence of effective prevention and treatment, the unmet medical need in the RSV-infected HSCT recipient population is substantial. Ideally, new antiviral treatments should target the virus early in the course of disease and prior to progression from RSV URTI to LRTI, as this would positively affect the clinical course of RSV infection.[36,44]

Adolescents who have undergone HSCT are similarly affected by the morbidity and mortality associated with RSV. Therefore, adolescents ≥13 to <18 years of age, who received a HSCT transplant, who are infected with RSV, and who meet the eligibility criteria may be enrolled in the adolescent cohort to allow generating some efficacy and safety data in adolescents, which may be used to support the use of JNJ-53718678 in adolescents. Furthermore, JNJ-53718678 has already been studied in the pediatric population with a trend towards an early antiviral effect of JNJ-53718678 and an acceptable safety profile (see Section 2.2). A Phase 2 study of JNJ-53718678 in the pediatric population is currently ongoing. No target sample size will be determined for the

adolescent cohort due to the expected low prevalence of such individuals in the overall HSCT recipient population.[3,7,10,57]

4.2.2. Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. The use of placebo is considered important for the proper evaluation of the safety and efficacy of JNJ-53718678 as a treatment for RSV infection (ICH E10 Guidance 2000). Apart from ribavirin or IVIG, which are not approved for use in this population, are not commonly used, are of uncertain efficacy, and subject to stratification (adult cohort only) in this study, no other specific treatments are available. Therefore, the current SOC for the treatment of RSV is supportive and may include administration of bronchodilators by aerosol, fluids, nutrition, and oxygen. A comparison of JNJ−53718678 to placebo on a background of SOC supportive therapy is thus not only justifiable, but essential to enable an objective determination of the potential benefits and risks of treatment with JNJ-53718678. Furthermore, patients randomized to placebo may benefit from the more extensive clinical care provided within the context of a clinical study.

Randomization within the adult and adolescent cohorts will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. The current design of this study includes a 2:1 randomization scheme. This design ensures that the number of participants randomized to the placebo group is minimized, while still enabling proper assessment of the clinical outcomes, safety, and antiviral activity of JNJ-53718678. Consequently, most participants in the study will receive JNJ−53718678 and thus have the potential to benefit from its antiviral activity, while the placebo group will allow comparison of the safety/tolerability with versus without treatment.

Stratification in the adult cohort will account for baseline characteristics where a significant treatment effect was seen in the presatovir URTI study (NCT02254408)[8,45] , ie, lymphopenia (<200, 200 to <500 cells/µL, and ≥500 to <1000 cells/µL) and hospitalization status at baseline (yes/no). Additionally, a third stratification factor will be pre-baseline use of ribavirin and/or IVIG (yes/no), given the uncertain efficacy of ribavirin and/or IVIG in RSV infection and accounting for the use of ribavirin and/or IVIG as components of SOC for RSV infection in HSCT recipients at some sites. No stratification will be applied to the adolescent cohort, due to the expected low number of participants in this cohort.

Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

4.2.3. Biomarker Collection

Blood samples will be collected for exploratory biomarker analyses (host RNA and/or proteins), on the premise that these markers may play a role in the treatment response, PK, safety of JNJ-53718678, or the status and course of RSV-related disease. In addition, leftover bilateral

mid-turbinate nasal swab or blood samples may be used for biomarker analysis (eg, proteins including cytokines).

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

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

4.2.4. Medical Resource Utilization

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

4.2.5. Participant Input Into Design

Participants were not involved in the design of this study.

4.2.6. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent 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 participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily will be enrolled.

The primary ethical concern is the use of placebo in this population. The rationale for using placebo is outlined in Section 4.2.2.

Other ethical concerns are the potential burden with obtaining lower respiratory tract samples (by bronchoscopy or inducing sputum) and the radiation exposure associated with imaging procedures (as part of screening and to identify potential RSV LRTI, as specified in Section 9.6). However, these assessments would be performed as part of SOC and do not expose the participant to additional risk above that from SOC. The additional radiation exposure from the screening chest X-ray, if not performed as SOC, is limited.

The total blood volume (maximum approximately 110 mL) to be collected is considered to be acceptable.

4.3. Justification for Dose and Duration

4.3.1. Study Intervention Dose

Participants will be administered 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors), 125 mg bid for 21 days (when coadministered with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole), and 125 mg qd for 21 days (when coadministered with posaconazole) as oral suspension of JNJ-53718678, or the same volume of placebo suspension. For newly enrolled participants after implementation of

Protocol Amendment 6, study intervention will be administered as 125 mg oral film-coated tablets or matching placebo (see Section 6.1). Please refer to Section 2.2 for details on the interaction with CYP3A4 inhibitors and Section 6.6 for details on CYP3A4 inhibitors that are allowed but require dose adjustment.

The initially selected JNJ-53718678 500 mg qd dosing regimen for Study 53718678RSV2005 was based on the results of the human challenge Study 53718678RSV2001, in which target engagement for JNJ-53718678 was demonstrated in immunocompetent adults inoculated with RSV-A Memphis 17b.[14] In Study 53718678RSV2001, 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 qd) as compared to the placebo group, without an apparent exposure-antiviral effect relationship. The protein-adjusted 90% effective concentration ($paEC_{90}$) of JNJ-53718678 against the RSV-A rgRSV224 strain was calculated as 41.0 ng/mL. The doses of 75, 200, and 500 mg qd had mean C_{trough} levels of 50, 85, and 334 ng/mL and were all above the $paEC_{90}$. Since all dose regimens were generally safe and well tolerated, the highest dose of 500 mg qd was selected for this study to minimize the risk of development of resistance and to ensure the highest potential for antiviral effect in the HSCT population. Doses of 500 mg qd will provide trough levels of at least 8 to 13-fold higher than $paEC_{90}$ levels (mean [SD] C_{trough} levels on Day 7 of 550 [477] ng/mL and 334 [197] ng/mL, as observed in Studies 53718678RSV1001 [n 6] and 53718678RSV2001 [n 18], respectively). In addition, as a direct-acting antiviral drug, the antiviral effects of JNJ-53718678 are projected to be independent of non-PK host factors such as immune status or age.[17] Efficacy of JNJ-53718678 in all populations is assumed to be primarily dependent on achieving a target plasma exposure. An HSCT recipient may have deficiencies in immune-mediated clearance of free virions and clearance of infected epithelial cells, processes not affected by JNJ-53718678. A longer treatment duration (see Section on Study Intervention Duration) is necessary in the HSCT population to compensate the reduced ability of their immune system to clear infected cells.

The dose (and qd dosing) initially selected for Study 53718678RSV2005 was also evaluated as the highest dose in Study 53718678RSV2004, in immunocompetent adults.

Population PK simulations of JNJ-53718678 in adult and pediatric participants (allometric scaling is included in the model on clearances and distribution volumes) have demonstrated that adolescent exposures largely overlap with adult exposures, indicating that 500 mg qd dosing for 21 days is appropriate for adolescents. Therefore, the dosing regimen in adolescents will be the same as the one in adults.[40]

Overall, based on all available data (see also the most recent edition of the IB and any Addenda),[34] it was anticipated that the initially proposed dose would be in the therapeutic range of JNJ-53718678 for HSCT recipients, with a favorable safety profile.

However, due to exposure (C_{max})-related important potential risk of QT interval prolongation identified from the analysis of the TQT Study 53718678RSV1009, the sponsor has performed additional modelling to evaluate alternative dose and dosing regimens, which would allow to maintain the plasma concentration (C_{trough}) at effective levels and maintain AUC exposure while

reducing the C_{max}, to mitigate this potential risk. The updated popPK model is suitable for PK simulations to adequately predict C_{max}, AUC, and C_{trough} after single and multiple doses of JNJ-53718678.

The physiologically-based pharmacokinetic (PBPK) model developed to assess the potential drug-drug interactions with JNJ-53718678 as victim was updated in SimCYP V19 to investigate the effect of concomitant administration of strong and moderate CYP3A4 inhibitors on the single-dose and steady-state C_{max} and AUC of JNJ-53718678 following dosing (Table 4). Based on the analyses, the use of moderate or strong CYP3A4 inhibitors has a similar effect on steady-state C_{max} (1.5-fold), albeit a different effect on steady-state $AUC_{0\ 24h}$ (up to 2-fold for moderate CYP3A4 inhibitors and up to 3-fold for strong CYP3A4 inhibitors).

Table 4: Simulated Effect of Concomitant CYP3A4 Inhibitors on JNJ-8678 PK Parameters

PK Parameter	Strong CYP3A4 Inhibitors[a]	Moderate CYP3A4 Inhibitors[b]
C_{max} single dose	1.5-fold	1.5-fold
AUC_{24h} single dose	3-fold	2-fold
C_{max} multiple doses	1.5-fold	1.5-fold
AUC_{24h} multiple doses	2.5-fold	2-fold

PK: pharmacokinetic, CYP: cytochrome P450, $AUC_{0\text{-}24h}$ = area under the plasma concentration-time curve from time of administration up to 24 hours postdose, $C_{max:}$ maximum plasma concentration.
Note: The effect of strong inhibitors on AUC single dose and AUC multiple dose was also evaluated as 3.5-fold. (Based on single-dose PK results of Study 53718678RSV1006. In this scenario, the effect of CYP3A4 induction on comedication is excluded).
[a] Based on itraconazole simulations.
[b] Based on eg diltiazem simulations.

Simulations were conducted using the popPK model, the effect of comedication and the ΔΔQTcI in the model (taking into account variance-covariance matrix of the drug-effect slope, plasma effect site equilibration rate constant [Ke_0] and intercept) with 1,000 virtual adult participants re-sampled from the 53718678RSV2004 data. The summary statistics of the simulation are presented in Table 5.

Table 5: Predicted Geometric Mean AUC_{0-24h}, C_{max}, C_{trough} and ΔΔQTcI After Day1 and Day 7

PK Parameters	250 mg bid	125 mg bid + moderate CYP3A4 inhibitors[a]	125 mg bid + strong CYP3A4 inhibitors
AUC_{0-24h} Day 1 (ng.hr/mL)	24,700	23,300	35,000[a]/40,800[b]
AUC_{0-24h} Day 7 (ng.hr/mL)	40,700	35,800	44,800[a]/62,700[b]
C_{max} Day 1 (ng/mL)	1,950	1,430	1,430
C_{max} Day 7 (ng/mL)	2,560	1,780	1,780
C_{trough} Day 1 (ng/mL)	710	623	935
C_{trough} Day 7 (ng/mL)	1,070	881	1,100
ΔΔQTcI Day 1 (ms) (90%CI)	2.98 (1.69-5.06)	2.66 (1.49-4.53)	2.66 (1.49-4.53)
ΔΔQTcI Day 7 (ms) (90%CI)	4.12 (2.10-7.66)	2.95 (1.48-5.61)	2.95 (1.48-5.61)

ΔΔQTcI: placebo-corrected change from baseline for the individual-corrected QTc, AUC_{0-24h}: AUC from time of administration up to 24 hours post dosing, bid: twice daily, CI: confidence interval, C_{max}: maximum plasma concentration, C_{trough}: predose plasma concentration, CYP: cytochrome P450, PBPK: physiologically-based pharmacokinetic(s), PK: pharmacokinetic(s).
a. Based on PBPK modeling.
b. Based on single dose PK results of 53718678RSV1006.

In Study 53718678RSV1001, the 250 mg bid regimen provided C_{trough} levels that are somewhat higher than those observed with the 500 mg qd regimen (mean [SD] C_{trough} levels on Day 7 of 550 [477] ng/mL and 643 [126] ng/mL [n 6] for 500 mg qd and 250 mg bid, respectively). The dose regimen of 250 mg bid provides similar exposure levels ($AUC_{0\ 24h}$), higher C_{trough} levels and lower C_{max} levels compared to the 500 mg qd regimen, which should translate to at least similar efficacy of JNJ-53718678 as well as maintain the favorable safety profile.

Based on final PK, QTc, and PBPK modeling (for interaction with moderate and strong CYP3A4 inhibitors), a 21-day dosing regimen of 250 mg bid is selected. The dose is to be reduced to 125 mg bid when patients are coadministered or may require initiation of moderate or strong CYP3A4 inhibitors, including macrolide antibiotics and antifungals, which are important in the population with high risk of RSV disease progression and complications. The upper limit of the 90% CI for ΔΔQTcI for the bid regimen in combination with moderate or strong CYP3A4 inhibitors remains below 10 ms for each of the groups (Table 5).

Overall, based on all currently available data, it is anticipated that the selected bid dosing of JNJ-53718678 will be in the therapeutic range for adults, ensuring the highest potential antiviral effect while minimizing the risk of development of resistance (resulting from increasing C_{trough} [mean C_{trough} will exceed more than 10 times the $paEC_{90}$ of 41 ng/mL]), as well as mitigating the potential risk of QT interval prolongation (by decreasing C_{max}).

Based on PBPK analyses, the exposure at steady state of JNJ-53718678 after 250 mg JNJ-53718678 bid dosing without concomittant use of CYP3A4 inhibitors is similar to 125 mg once daily dosing with coadministration of posaconazole (400 mg bid) and similar to 125 mg JNJ-53718678 bid dosing with co-administration of voriconazole (200 mg bid), or clarithromycin (500 mg bid) or itraconazole (200 mg qd).

4.3.2. Study Intervention Duration

In immunocompetent adult and pediatric participants, a treatment duration of 7 days is used, as specified in Studies 53718678RSV2004, 53718678RSV2001, 53718678RSV1005, and 53718678RSV2002.[13,14,15,16] Because of the prolonged viral shedding[3,26] observed in HSCT recipients, the treatment duration will be 21 days in Study 53718678RSV2005. This is consistent with the presatovir URTI study (NCT02254408),[8] where an every 4-day dosing regimen for 5 total doses ensured adequate plasma levels for 21 days.

Currently, there are no clinical data available from a 21-day treatment with JNJ-53718678. This duration, however, is considered to be safe because:

- In Study 53718678RSV1002,[12] in which a dosing duration of 13 days was evaluated, steady state conditions were generally achieved at 8 days of dosing. This 13-day dosing regimen (500 mg qd) was generally safe and well tolerated.
- In Study 53718678RSV1001,[11] there was no accumulation of JNJ-53718678 observed in immunocompetent adult participants at 1 week of dosing. The anticipated exposure in Study 53718678RSV2005 with 500 mg qd is expected to be similar for HSCT recipients as has been observed in immunocompetent participants.
- A duration of 21 days of repeated dosing in patients is supported by 1-month repeat-dose good laboratory practice toxicology studies in adult rats and minipigs. Repeated dosing for 1 month in rats resulted in a No Observed Adverse Effect Level (NOAEL) of 75 mg/kg/day, associated with a mean (SD) maximum plasma concentration (C_{max}) of 3,240 (338) ng/mL and 9,240 (477) ng/mL in male and female rats, respectively, and a mean (SD) AUC_{24h} of 11,600 (849) ng.h/mL and 52,600 (990) ng.h/mL in male and female rats, respectively. In minipigs, repeated dosing for 1 month did not result in any treatment related effect (No Observed Effect Level [NOEL]) at 10 mg/kg/day, associated with a mean (SD) C_{max} of 1,510 (440) ng/mL and 1,750 (440) ng/mL in male and female minipigs, respectively, and a mean (SD) AUC_{24h} of 21,200 (870) ng.h/mL and 31,500 (8,350) ng.h/mL in male and female minipigs, respectively. Detailed results of the studies can be found in the most recent edition of the IB and any Addenda.[34] These NOAEL and NOEL exposures are in the same range as the values that were achieved with 500 mg qd in Study 53718678RSV1001[11] (mean [SD] C_{max}: 2,655 [591] ng/mL and mean [SD] AUC_{24h}: 31,165 [12,686] ng.h/mL).
- The IDMC will perform the first unblinded safety review prior to (should a safety signal warrant) or after the 18th patient has completed the Day 28 assessments (or discontinued earlier) to assure an early evaluation of the treatment duration.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit (phone visit or on-site visit) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the 1 year follow-up visit.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase (Day 21) will not be considered to have completed the treatment period.

5. STUDY POPULATION

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

Repeat testing, once for laboratory results and once for ECG results, is allowed for individuals who do not meet the criteria for participation in this study

5.1. Inclusion Criteria

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

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement).

2. 18 to 75 years of age, inclusive. Subjects ≥13 and <18 years of age may be enrolled in selected countries and study sites consistent with local regulations.

3. Received an autologous or allogeneic HSCT using any conditioning regimen.

4. ALC <1,000 cells/μL. The local assessment confirming ALC <1,000 cells/μL should be performed no more than 48 hours prior to randomization.

5. The participant has been diagnosed with RSV infection using a rapid PCR- or other molecular-based diagnostic assay performed on a bilateral mid-turbinate nasal swab sample as part of the study-specific screening assessment or on an upper respiratory tract sample as part of SOC testing.

   Note: Results from upper respiratory tract samples collected per local SOC testing within 24 hours prior to start of Screening may also be used for determining study eligibility. The SOC sample used for RSV diagnosis should have been collected no more than 48 hours prior to randomization.

6. New onset of at least 1 of the following respiratory symptoms within 4 days prior to the anticipated start of dosing (Day 1): nasal congestion, rhinorrhea, cough or pharyngitis (sore throat), and/or worsening of one of these chronic (associated with previously

existing diagnosis, eg, chronic rhinorrhea, seasonal allergies, chronic lung disease) respiratory symptoms within 4 days prior to the anticipated start of dosing (Day 1).

7. SpO_2 ≥92% on room air.

8. No evidence of new abnormalities consistent with LRTI on a chest X-ray relative to the most recent chest X-ray, as determined by the local radiologist (preferentially) or the investigator. A chest X-ray should be performed no more than 48 hours prior to randomization. If a chest X-ray has not been obtained as part of SOC, it must be obtained during Screening.

9. Willingness to complete necessary study procedures

10. Except for the RSV-related illness, the participant must be medically stable based on physical examination, medical history, and vital signs performed at Screening. If there are abnormalities, they must be consistent with the underlying condition in the study population as evaluated by the investigator. This determination must be recorded in the participant's source documents and initialed by the investigator.

11. Must sign an ICF/assent form indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

    Note: Prior to signing the main consent/assent form for the study, the participant may specifically allow for the collection and testing of a bilateral mid-turbinate nasal swab sample by signing the pre-Screening (diagnostic) ICF/assent form. This is not required if an upper respiratory sample is collected for diagnostic testing per local SOC.

12. Criterion modified per Amendment 2.

12.1 A woman must be (as defined in Appendix 10.5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information)

   a. Not of childbearing potential
   b. Of childbearing potential and
      - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of relevant systemic exposure. Examples of highly effective methods of contraception are located in Appendix 10.5. Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
      - Have a negative highly sensitive serum (β-human chorionic gonadotropin) local pregnancy test at Screening.

13. 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 intervention.

14 Criterion modified per Amendment 2.

14.1 From Day 1 during the study and for 90 days after receiving the last dose of study drug, a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person throughout the study. Male participants 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.

15. A male participant 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 intervention.

16. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

17. Must have been assessed per local public health practice and considered not to have SARS-CoV-2 infection during this respiratory infection.

5.2. Exclusion Criteria

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

1. Admitted to the hospital primarily for a lower respiratory tract disease of any cause as determined by the investigator.

2. Requires supplemental oxygen at Screening or any time between Screening and randomization.

3. History of or concurrent illness that in the opinion of the investigator might confound the results of the study or pose an additional risk in administering study intervention to the participant or that could prevent, limit, or confound the protocol-specified assessments.

4. Documented to be positive for other respiratory viruses (limited to influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, or coronavirus) within 7 days prior to or at the Screening visit, if determined by local SOC testing (additional testing is not required).

5. Clinically significant bacteremia or fungemia within 7 days prior to or at Screening that has not been adequately treated, as determined by the investigator.

6. Bacterial, fungal, or viral pneumonia within 2 weeks prior to Screening that has not been adequately treated, as determined by the investigator.

7. Known history of HIV/AIDS with a $CD4^+$-cell count <200 cells/µL within the last month.

8. Known allergies, hypersensitivity, or intolerance to JNJ-53718678 or its excipients (refer to Investigator's Brochure).

9. Had major surgery (other than HSCT) within 28 days prior to randomization or has planned major surgery through the course of the study.

10. Has known aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3x upper limit of normal within the 4 weeks prior to Screening.

11. Has known or suspected clinically active chronic or acute hepatitis B or C infection.

12. Criterion modified per Amendment 1.

12.1 Current or planned participation in another clinical study where study intervention is being administered while participating in the current study. ***Note:*** Concurrent enrollment is allowed during the follow-up phase of the other clinical study or in case the study intervention in the other clinical study is a marketed product already approved for another indication, and taking into account the restrictions as specified in Section 6.6.

13. Unwilling to undergo bilateral mid-turbinate nasal swab procedures or with any physical nasal abnormality, which limits the ability to collect regular nasal specimens.

14. Criterion modified per Amendment 6.

14.1 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 intervention ingestion or absorption. ***Note:*** During hospitalization, the drug (oral suspension or oral film-coated tablets dispersed in water) can be administered through a nasogastric tube, if already in place.

15. Has taken any disallowed therapies as noted in Section 6.6, Concomitant Therapy before the planned first dose of study intervention.

16. Criterion modified per Amendment 1.

16.1 Received an investigational RSV vaccine at any time prior to the study or used an invasive investigational medical device within 30 days prior to the study.

17. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

18. Criterion modified per Amendment 3.

18.1 Confirmed QTcF interval >450 milliseconds per the machine read parameter result at Screening. Presence of an abnormal QTcF interval should be confirmed by repeat ECG recording during Screening.

19. Criterion modified per Amendment 3.

19.1 Criterion modified per Amendment 5.

19.2 Clinically significant abnormal ECG findings (other than QTcF interval >450 milliseconds, see exclusion criterion 18) not consistent with the underlying condition in the study population, as judged by the investigator based on the machine read ECG results at Screening.

20. Employee of the sponsor, investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as direct family members of the employees or the investigator.

21. Has evidence of one of the following ECG abnormalities per the machine read ECG results at Screening confirmed by repeat ECG recording:

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

22. Criterion combined with exclusion criterion 19 per Amendment 5.

23. Has had ANY of:

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

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

24. Has a personal or first- or second-degree family history of long QT syndrome or sudden cardiac death.

25. Has a ≥Grade 3 laboratory abnormality of hypokalemia of <2.5 mEq/L and/or hypomagnesemia of <0.9 mEq/L at Screening (or 4 days prior to Screening). If the Grade 3 laboratory abnormality is not confirmed (repeat local test during Screening), the participant may be enrolled.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 10.3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle 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 electronic patient-reported outcomes (ePRO) measures (RiiQ, PGI) and the completion of the other ePRO measures per Schedules of Activities.

3. Concurrent administration of authorized medications or prophylactic vaccines/use of licensed devices is allowed as supportive therapy or as prophylaxis per local SOC and package inserts, as long as the medication/vaccine/device will not affect the participant's participation in the study and is in accordance with allowed concomitant therapy (see Section 6.6). Also, an investigational drug from another clinical study is allowed in case it is a marketed product, ie, approved for another indication.

   Refer to Section 6.6 for details regarding prohibited and restricted therapy during the study.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent/assent.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if they experience a new URTI episode. Rescreened participants should be assigned a new participant number as for the initial screening.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Eligible participants will be randomized 2:1 (active:placebo) within each cohort to receive either JNJ-53718678 or placebo for 21 days. Participants will be administered 250 mg JNJ-53718678 bid for 21 days (without coadministration with moderate or strong CYP3A4 inhibitors), 125 mg bid for 21 days (when coadministered with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole), and 125 mg qd for 21 days (when coadministered with posaconazole) as oral suspension of JNJ-53718678, or the same volume of placebo suspension. For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be administered as 125 mg oral film-coated tablets or matching placebo (see Table 6 and Section 6.5). Please refer to Section 2.2 for details on the interaction with CYP3A4 inhibitors and Section 6.6 for details on CYP3A4 inhibitors that are allowed and coadministration with posaconazole.

Table 6: Treatment Overview

Treatment	Dosing Regimen	Formulation[d]
A	250 mg JNJ-53718678[a] twice daily for 21 days without coadministration with moderate or strong CYP3A4 inhibitors	12.5 mL oral suspension[b] of JNJ-53718678 or 2 eq. 125 mg oral film-coated tablets[c]
A	125 mg JNJ-53718678[a] twice daily for 21 days if coadministration with moderate or strong CYP3A4 inhibitors, with the exception of posaconazole	6.25 mL oral suspension[b] of JNJ-53718678 or 1 eq. 125 mg oral film-coated tablet[c]
A	125 mg JNJ-53718678[a] once daily for 21 days if coadministration with posaconazole	6.25 mL oral suspension[b] of JNJ-53718678 or 1 eq. 125 mg oral film-coated tablet[c]
B	Matching placebo twice daily for 21 days	12.5 mL matching placebo suspension or 2 matching oral placebo tablets
B	Matching placebo twice daily for 21 days	6.25 mL matching placebo suspension or 1 matching oral placebo tablet
B	Matching placebo once daily for 21 days	6.25 mL matching placebo suspension or 1 matching oral placebo tablet

a. Doses are provided for JNJ-53718678-AAA.
b. JNJ-53718678 is dosed as an oral suspension containing 23 mg/mL JNJ-53718678-ZCL, the hemi-tartrate salt of JNJ-53718678-AAA, which is equivalent to 20 mg/mL JNJ-53718678-AAA.
c. For newly enrolled participants after implementation of Protocol Amendment 6, the drug product is administered as eq. 125 mg oral film-coated tablets (containing 143.75 mg of JNJ-53718678-ZCL, the hemi tartrate of JNJ-53718678-AAA). Note that the tablet may also be dispersed in water before administration through a nasogastric tube, if applicable.
d. A participant receiving oral suspension must complete the study with the same formulation.

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

Study intervention will be administered orally. Dosing should preferably occur approximately at the same time each day (for the qd dosing and for the AM and PM dosing of the bid regimen).

For participants on bid dosing, dosing should occur approximately 12 hours apart. For participants who receive the first dose of study intervention PM of Day 1, dosing should continue through the morning (ie, AM) of Day 22 so that all participants receive 42 consecutive bid doses in total. Administration of the second bid dose may be delayed or brought forward (by maximum 4 hours)

only if the nominal timing for this second dose falls in the middle of the night; thereafter, further dosing will follow a regular AM/PM dosing schedule.

Participants on a 125 mg qd regimen coadministered with posaconazole will receive 21 consecutive doses in total.

The study intervention can be administered with or without food. During hospitalization, the drug (oral suspension or oral film-coated tablets dispersed in water) can also be administered through a nasogastric tube, if already in place.

The first dose of study intervention will be administered at the study site on Day 1; date and time of dosing study intervention must be captured in the source documents and the electronic case report form (eCRF). Other dosing dates will be captured in the eCRF on study visit days. Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol and how to withdraw the appropriate volume from the vial. For newly enrolled participants after implementation of Protocol Amendment 6, study intervention will be supplied as oral film-coated tablets in bottles. Each bottle contains a sufficient number of tablets to cover study intervention for at least 7 days. During (re)hospitalization, study intervention will be administered by the study-site personnel. At home, or when the rehospitalization occurs at a non-study site, study intervention will be administered by the participant or their caregiver.

JNJ-53718678 and matching placebo will be manufactured and provided under the responsibility of the sponsor.

For a definition of study intervention overdose, refer to Section 8.5, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Oral Suspension

The drug product is supplied as a 1,988-mg/bottle powder and solvent for oral suspension (G007 and G005, respectively). The powder (which consist of API only) will be reconstituted with the solvent to obtain a 23-mg/mL oral suspension (equivalent to 20-mg/mL oral suspension of JNJ-53718678-AAA [free form]).

The placebo drug product is supplied as a 4,940-mg/bottle microcrystalline cellulose powder and solvent for oral suspension (G008 and G003, respectively). The placebo powder will be reconstituted with the solvent to obtain a placebo oral suspension.

For a list of excipients for the solvents for oral suspension, refer to the most recent edition of the IB and any Addenda for JNJ-53718678.[34]

Suspended study intervention will be provided to participants in vials, from which a defined volume is to be withdrawn (see Table 6). Each vial contains study intervention for at least a 3-day

dosing period. All study intervention should be stored on site and at home as instructed on the label.

Refer to the pharmacy manual/study site Investigational Product Preparation Instruction (IPPI) for additional guidance on study intervention preparation, handling, and storage.

Oral Film-coated Tablets (After Implementation of Protocol Amendment 6)

The drug product is supplied as eq. 125 mg oral film-coated tablets (G033; containing 143.75 mg of JNJ-53718678-ZCL, the hemi tartrate of JNJ-53718678-AAA, equivalent to 125 mg JNJ-53718678-AAA, the free from drug substance) or matching oral placebo film-coated tablets (G037).

For a list of excipients of the tablet, refer to the most recent edition of the IB and any addenda for JNJ-53718678.[34]

JNJ-53718678 oral film-coated tablets will be manufactured and provided under the responsibility of the sponsor.

Study intervention will be provided to participants in bottles. Each bottle contains a sufficient number of tablets to cover study intervention for at least 7 days.

The tablet may also be dispersed in water before administration through a nasogastric tube, if applicable. Refer to the pharmacy manual/study site IPPI for additional guidance on study intervention preparation and handling in case of administration through nasogastric tube.

Accountability

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 interventions (Treatments A and B; 2:1 [active: placebo] randomization) groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. In the adult cohort, the randomization will be balanced by using randomly permuted blocks and will be stratified by hospitalization status (yes/no) at the time of randomization, lymphopenia (<200 cells/µL, 200 - <500 cells/µL, and ≥500 - <1,000 cells/µL) at Screening, and ribavirin and/or IVIG use (yes/no) at the time of randomization. No stratification will be applied to the adolescent cohort.

Participants with an ALC <500 cells/µL at Screening should account for at least 50% of all enrolled participants in the adult cohort and participants with an ALC <200 cells/µL at Screening should account for at least 25% of all enrolled participants in the adult cohort, also at the time of the interim analysis. To ensure the prespecified distribution in the strata, enrollment in the stratum ALC >500 cell/µL or 200 - <500 cells/µL may be paused prior to the interim analysis and closed prior to the final analysis (see Section 9.3).

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kits for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS.

Blinding

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

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 intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis (see Section 9.4.10).

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

6.4. Study Intervention Compliance

The study intervention will be administered orally. During hospitalization, study intervention will be administered by the study-site personnel. The study intervention (oral suspension or oral film-coated tablets dispersed in water) can also be administered through a nasogastric tube, if already in place.

Outpatients will receive instructions on compliance with study intervention administration. In case of (re)hospitalization during the study, this instruction will be repeated at the time of discharge, if applicable. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any participant who is not compliant with taking in the study intervention.

If participants are (re)hospitalized due to worsening of RSV disease during the treatment period, administration of study intervention should continue.

If the participant vomited shortly after intake of study intervention, the participant should not be re-dosed for that administration timepoint.

In case a dose was missed, the dose should be given as soon as possible, but:

- For bid dosing: within 6 hours after the scheduled time. If more than 6 hours have elapsed, the dose should be skipped, and the next dose should be given at the next scheduled timepoint per the initial dosing schedule.
- For qd dosing: 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 timepoint per the initial dosing schedule.

6.5. Dose Modification

In case comedication of the class of strong or moderate CYP3A4 inhibitors is started or continued during study intervention treatment, the dose needs to be adjusted to 125 mg bid unless comedication of posaconazole is started or continued in which case further dose adjustment to 125 mg qd is needed (see Sections 4.3.1, 6.1, 6.5, and 6.6). When this comedication is stopped during the study intervention administration period, study intervention dosing must be resumed at

the 250 mg bid regimen. See Section 8.4.7.2 for the required cardiac safety monitoring in such cases.

6.6. Concomitant Therapy

Concomitant medications, except those listed below, are allowed during this study. All concomitant medications and supportive therapy (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements, or physiotherapy) different from the study intervention must be recorded in the eCRF, from the date the main study ICF is signed through to the end-of-study visit. Recorded information will include a description of the type of the drug/therapy, treatment duration (dates of treatment start and stop), dose regimen, route of administration, and its indication. If a participant has received acute doses of a prohibited drug, switching to an alternative drug chosen at the discretion of the investigator will be allowed. Modification of an effective pre-existing chronic therapy should not be made for the explicit purpose of entering a participant into the study.

Immunosuppressants (IS) and other therapy for the treatment of the HSCT status of the participant should be continued, taking into account the respective package inserts. As JNJ-53718678 is a weak inducer and a weak inhibitor of CYP3A4, there is a potential for interaction between JNJ-53718678 and IS drugs that are CYP3A4 substrates (eg, sirolimus, cyclosporine, and tacrolimus), similar to the time-dependent effects observed with midazolam (see Section 2.2). It is recommended that therapeutic drug monitoring of such IS is performed to assure adequate immunosuppressant exposures and to allow for IS dose adjustments. In case therapeutic drug monitoring is performed as part of SOC or per protocol instruction, the measured IS exposures are to be captured in the eCRF.

Participants 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. In case antipyretics are used, body temperature should be measured immediately before or >4 hours after giving antipyretics.

Fexofenadine is allowed, taking into account its package insert and dosing instructions, but JNJ-53718678 may reduce the fexofenadine exposure by 65% and reduce its efficacy if administered simultaneously. To limit the reduction in efficacy, it is recommended to administer fexofenadine at least 1 to 2 hours before taking JNJ-53718678 and/or at least 4 hours after taking JNJ-53718678, taking into account the local prescribing info for fexofenadine.[29,31]

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

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

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

The use of ribavirin and IVIG is allowed during the study if considered SOC for the HSCT recipient population per local guidelines.

As side effects due to seasonal (eg, influenza) or other routine (eg, pneumococcal) vaccination, as well as due to COVID-19 vaccination (locally-approved [including emergency use-authorized] vaccines) may impact the evaluation of clinical evolution of RSV symptoms, it is recommended that administration of these prophylactic vaccines be timed to occur after study completion or at least 1 week after the last dose of study medication (study Day 28). Investigator discretion, considering the vaccine package insert and local clinical practice guidelines, including postponing the vaccination for participant suffering from acute infection or febrile illness, and overall assessment of clinical stability will be relied on if there is a medical need to administer vaccine to a participant during the study period. Study intervention administration as well as visits and assessments can continue as scheduled.

The following medications are not permitted from Screening through 3 days after the last dose of JNJ-53718678 and for the time period prior to Screening as noted:

- herbal supplements with active metabolic enzyme inducing components (eg, St. John's Wort) within 21 days or breast cancer resistance protein (BCRP, a transporter protein) inhibiting components (eg, curcumin) within 2 days prior to randomization. This does not apply to herbal teas, herbal supplements without confirmed strong CYP3A4 inhibitory/inductive activity, and/or homeopathy.
- palivizumab, within 5 half-lives (approximately 100 days) prior to screening.
- any investigational RSV vaccine at any time prior to the study or an invasive investigational medical device within 30 days before the planned first dose of study intervention.
- any other study intervention, unless if the study intervention in another clinical study is a marketed product already approved for another indication. Note: Concurrent enrollment is allowed during the follow-up phase of another clinical study.
- prescription medications that are known to be strong inducers of CYP3A4 such as, but not limited to, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin. Note: moderate inducers such as bosentan, efavirenz, etravirine, glucocorticoids, and modafinil are allowed.
- prescription medications that are known to be BCRP inhibitors including eltrombopag, fostamatinib, rolapitant, and teriflunomide within 5 times their respective half-lives prior to randomization.
- prescription medications with a known risk to prolong the QT interval (eg, azithromycin, see Table 7). Note: these medications can be continued if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Prescription medications which are known to be a moderate or strong inhibitor of CYP3A4 enzymes as listed in Table 7 are allowed with dose reduction. If several medications for the same indication are available and can be used interchangeably, it is recommended to administer the drug with the least CYP3A4 inhibitory potency.[30].

Note: in case of doubts about the CYP3A4 enzymes inhibitory or inducing capacity, it is recommended to contact the sponsor.

Table 7: Examples of Commonly Used Medications With CYP3A4 Inhibiting and/or QT Prolonging Effects Which are Disallowed or Allowed Upon Coadministration with JNJ-53718678[f]

Drug Class	CYP3A4 Inhibitors Allowed with JNJ-53718678 Dose Reduction[a]	QT Prolonging Drugs Allowed with Restrictions[b]	CYP3A4 Inhibitors + QT Prolonging Drugs Allowed with JNJ-53718678 Dose Reduction and Restrictions[c]	CYP3A4 Inhibitors + QT Prolonging Drugs Allowed with JNJ-53718678 Dose Reduction[d]	CYP3A4 Inhibitors/Inducers +/- QT Prolonging Drugs Disallowed[e]
Antifungals	itraconazole, isavuconazole, ravuconazole	pentamidine	fluconazole, voriconazole	posaconazole	ketoconazole
Macrolide antibiotics	troleandomycin	azithromycin	clarithromycin, erythromycin		
Ketolide antibiotics	telithromycin				
Fluoroquinolones		levofloxacin, moxifloxacin	ciprofloxacin,		
Antidepressants	nefazodone				
Calcium channel blocker	verapamil				
Immunomodulators	cyclosporine				
Anti-arrhythmics		disopyramide, procainamide, quinidine, sotalol			amiodarone, flecainide, mexiletine, propafenone, systemic lidocaine
Antipsychotics		haloperidol, thioridazine, ziprasidone			
Antidepressants		citalopram, escitalopram			
Antiemetics		dolasetron, droperidol, granisetron, ondansetron			
Antihistamines					astemizole, terfenadine
Gastrointestinal/ gastroesophageal reflux disease drugs					cisapride

Table 7: Examples of Commonly Used Medications With CYP3A4 Inhibiting and/or QT Prolonging Effects Which are Disallowed or Allowed Upon Coadministration with JNJ-53718678[f]

Drug Class	CYP3A4 Inhibitors Allowed with JNJ-53718678 Dose Reduction[a]	QT Prolonging Drugs Allowed with Restrictions[b]	CYP3A4 Inhibitors + QT Prolonging Drugs Allowed with JNJ-53718678 Dose Reduction and Restrictions[c]	CYP3A4 Inhibitors + QT Prolonging Drugs Allowed with JNJ-53718678 Dose Reduction[d]	CYP3A4 Inhibitors/Inducers +/- QT Prolonging Drugs Disallowed[e]

This list is not exhaustive. Investigators must consult with the sponsor for any additions or updates to this list. For medications with a known risk to prolong the QT interval investigators are referred to the complete list available at https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf. Investigators must check regularly for any additions or updates to this list.

a. Dose reduction of JNJ-53718678 required in case of comedication of JNJ-53718678 with strong or moderate CYP3A4 inhibitors (see Sections 6.1 and 6.5).
b. Medications with a known risk to prolong the QT interval can be continued if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, however, the use of these medications cannot be initiated at screening and/or during the study intervention treatment period.
c. Medications with CYP3A4 inhibitory effects in addition to QT interval prolonging effects are allowed if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, but this requires dose adjustment of JNJ-53718678 (see Sections 6.1 and 6.5). These medications can also be started during the treatment intervention period with additional cardiac safety monitoring (see Section 8.4.7.2).
d. Posaconazole is allowed if the participant is already on a stable therapy prior to screening and if the QT interval meets the eligibility criteria, but this requires dose adjustment of JNJ-53718678 (see Sections 6.1 and 6.5). When posaconasole is started during the treatment intervention period, dose adjustment (see section 6.1 and 6.5) and additional cardiac safety monitoring (see Section 8.4.7.2) must be performed.
e. Disallowed within 14 days prior to screening and during the study.
f. If several medications for the same indication are available and can be used interchangeably, it is recommended to administer the drug with the least CYP3A4 inhibitory potency.

6.7. Intervention After the End of the Study

If the information on (an) ongoing AE(s) is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the eCRF.

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent/Assent in Appendix 10.3, Regulatory, Ethical, and Study Oversight Considerations).

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine SOC.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent or assent to receive study intervention
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- The participant becomes pregnant
- The participant has a confirmed QTcF interval ≥500 milliseconds at any scheduled visit, per the machine read parameter result. Confirmation needs to be obtained as soon as possible during the same visit by another machine read ECG.
- The participant has a confirmed (repeat local test) laboratory abnormality of hypokalemia of <2.5 mEq/L and/or hypomagnesemia of <0.9 mEq/L in samples taken any time throughout the study intervention treatment period (see also Section 8.4.7.2). Repeat sampling (local laboratory) to be performed within 24 hours of the result being available at the site.
- The participant is reported with the following laboratory abnormalities: AST or ALT increases ≥3 x ULN in samples taken at Screening, confirmed in a repeat test, to be performed within 48 hours of the result being available at the site.
- After start of study intervention, the participant is reported with (confirmed) liver function related laboratory abnormalities as indicated in Appendix 10.6, unless these are related to newly developing GVHD per investigator's evaluation.
- After start of study intervention, and applicable in case of GVHD, the participant is reported with the following laboratory abnormalities:

  AST or ALT increases >5 x ULN and rising with or without total bilirubin increase >2 x ULN

  AST or ALT remains >5 x ULN without a change in total bilirubin for more than 2 weeks

- After start of study intervention, subject develops Grade 3 rash or higher, which is suspected to be related to study intervention.

If a participant prematurely discontinues study intervention for any reason before the end of the Treatment Phase, the participant is recommended to remain compliant to all study-related procedures including timely completion of all efficacy assessments up to Day 49 or at least through Day 28 (see Schedules of Activities).

If the reason for discontinuation of study intervention is full withdrawal of consent/assent, refer to Section 7.2).

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be enrolled.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent or assent
- Death
- Decision by the sponsor to stop or cancel the study
- Decision by the investigator to withdraw participant
- Decision by local regulatory authorities and Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) to stop or cancel the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is full withdrawal of consent or assent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent/assent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

Prior to a participant withdrawing consent/assent for follow-up, the investigator should offer the participant an opportunity for an optional Withdrawal and Safety Follow-up Visits. At these optional Withdrawal and Safety Follow-up Visits, the same assessments as on the Day 22 and Day 28 visits, respectively, will be performed.

Withdrawal From the Use of Research Samples

The biomarker research samples collected in the study are mandatory, unless local regulations require these to be optional. In such case, a participant 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 participant's original separate informed consent/assent for optional research samples.
- The participant may withdraw consent/assent for optional research samples, 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/assent 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 participant may withdraw consent/assent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 10.3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Overview

The Schedules of Activities summarize the frequency and timing of efficacy, PK, clinical laboratory, and safety assessments as well as PRO, biomarker analysis, and MRU, applicable to this study.

PRO assessments should preferentially be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions, with the exception of the screening assessment, which can take place after clinician assessment of eligibility.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PRO, ECG, vital signs, bilateral mid-turbinate nasal swab, blood sampling, and physical examination. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Local pregnancy tests will be performed at timepoints indicated in the Schedules of Activities. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study and if experiencing a delayed menstrual period (over 1 month between menstrual cycles) or infrequent or irregular menstrual cycles to confirm absence of pregnancy.

Medical resource utilization data will be collected. Refer to Section 8.10, Medical Resource Utilization for details.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 110 mL over the duration of this study.

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

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. For hospitalized participants, if blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken.

Refer to the Schedules of Activities 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- JNJ-53718678 IB and any addenda
- Pharmacy manual, including study IPPI
- Study intervention
- Oral dosing syringes (only for oral suspension formulations)
- Laboratory manual
- ePRO completion guides
- ePRO participant information sheets, including FAQs
- eDevice and instructions for use
- IWRS Manual
- eCRF completion guidelines
- ECG machine and manual
- Additional auxiliary materials, as needed
- Specimen collection kits for PK, safety blood, and urine samples as well as bilateral mid-turbinate nasal swab samples
- Contact information page(s)

8.2. Efficacy Assessments

8.2.1. Development of Lower Respiratory Tract Infection/Complications

8.2.1.1. Chest Imaging

Evaluation of a chest X-ray at Screening is required for determining study eligibility (see Section 5.1). A chest X-ray should be collected prior to randomization. If a chest X-ray has not been obtained as part of SOC, it must be obtained during Screening and not more than 48 hours before randomization.

During the course of the study, it is anticipated that, as part of SOC and strongly recommended by the sponsor, investigators should perform chest imaging and/or CT scans, as well as other SOC assessments, if there is any suspicion of the occurrence of an LRTI, ie, development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough), as soon as possible. Outpatients must be instructed to contact the site immediately when there is a deterioration in their condition and should be invited for an unscheduled visit to be evaluated for the development of an LRTI.

Images and results from local reading for chest X-rays will be used for Screening and eligibility determination. Local reading should be performed by the local radiologist, unless the turnaround

time is very long, in which case the investigator can perform the interpretation to determine eligibility. In such case, the image may be sent to the EAC vendor for confirmatory central reading. Chest imaging done in randomized participants during the course of the study will be collected electronically from the site, sent to a central reader for review and interpretation, and stored electronically. For participants who experienced a suspected LRTI, all available reports (also from Screening) from the central and local readers and images will be sent for review to the EAC (see Section 9.6).

8.2.1.2. Lower Respiratory Tract Samples

If there is any suspicion of the occurrence of an LRTI, ie, development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough), leading to chest imaging, per local SOC a lower respiratory tract sample (eg, BAL, induced sputum, or regular sputum) should be obtained for microbiologic and virologic evaluation to determine the etiology. The reports of this evaluation will be provided to the EAC.

The determination of the presence of RSV or other respiratory pathogens in the lower respiratory tract sample may be performed locally as part of SOC, unless such testing is not locally available, in which case central testing for RSV may be performed.

If feasible, the leftover of the lower respiratory tract sample will be sent to the central laboratory for additional virologic analyses.

8.2.1.3. Bilateral Mid-turbinate Nasal Swab Samples

In case of clinical suspicion of the occurrence of an LRTI, an additional bilateral mid-turbinate nasal swab sample should be collected. If the collection of a bilateral mid-turbinate nasal swab sample is planned as part of the scheduled visit, collection of an additional sample in case of suspicion of LRTI is not required. This sample will be aliquoted and sent to the central laboratory for:

- RSV detection and RSV viral load
- viral sequencing

For a selected set of bilateral mid-turbinate nasal swab samples, quantitative RSV culture may be performed, if feasible, for determination of RSV infectious viral titer.

8.2.1.4. Blood Samples for RSV Viremia

In case of clinical suspicion of the occurrence of an LRTI, a blood sample for evaluation of RSV viremia will be collected for central analysis. At the discretion of the sponsor, leftover from these samples may be used for an exploratory analysis of other pathogens in blood.

8.2.1.5. Collection of Lower Respiratory Tract Infections Source Documentation for Endpoint Adjudication Committee Review

During the course of the study, the following results and reports from evaluations performed per SOC will be collected and will be reviewed by an EAC (see Section 9.6):

- images and reports from chest imaging, including the reports from the central reader (see Section 8.2.1.1)
- results of all local microbiology and virology tests performed (all bacterial, viral, fungal, parasite, or other results from any respiratory system-related sample [eg, BAL, sputum, pleural fluid, or lung tissue] and from blood specimens, including bacterial culture, virology [mostly by PCR], and serology studies)
- ECG tracings and reports of any ECG performed in relation to a suspected LRTI event
- body temperature
- clinical notes
- autopsy reports (if applicable)
- clinical course evaluations, including the specific reason for the repeat imaging
- other supporting documents, as requested.

All participant-related documents from the site should be anonymized.

8.2.2. Clinical Course of RSV Infection

The study will include the following evaluations of the clinical course of RSV infection at timepoints indicated in the Schedules of Activities:

- clinical parameters: respiratory rate, heart rate, SpO_2, and body temperature as measured by the investigator during scheduled visits
- respiratory signs and symptoms, including auscultation findings, as evaluated by the investigator
- requirement for supplemental O_2
- supplemental O_2 type (eg, supplemental oxygen, noninvasive pressure ventilation, endotracheal-mechanical ventilation), and duration
- (re)hospitalization by level of care during treatment and follow-up
- duration of (re)hospitalization and duration of ICU use
- respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and all-cause mortality
- Grade 3 and Grade 4 AEs in the Infections and Infestations System Organ Class
- respiratory and thoracic-related AEs
- the use of antibiotics in participants who develop RSV LRTI per the EAC's assessment and in participants who do not develop RSV LRTI

- duration and severity of RSV signs and symptoms, as assessed by the participant using the RiiQ Symptom Scale (see Appendix 10.9) and Patient Global Impression (PGI) questions (ie, PGI of Severity [PGI-S], PGI of Health [PGI-H], and PGI of Change in Health [PGI-C]; see Appendix 10.10). Symptoms reported in the RiiQ will not be reported as AEs but constitute a part of the efficacy evaluations. ***Note:*** LRTI symptoms, ie, development of a lower respiratory sign or symptom (including decrease in oxygen saturation or increase in supplemental oxygen to maintain oxygen saturation, wheezing, rhonchi, rales, dyspnea, tachypnea, worsening cough), reported by the participant in the RiiQ, will trigger the evaluation for suspected LRTI by the investigator.
- occurrence of GVHD or delayed engraftment as evaluated by the investigator

An electronic device (eDevice) to be used for the ePRO will be provided to the participants at Screening to record participant's ratings of the severity of their symptoms, as specified in the Schedules of Activities. The investigator/study staff will provide sufficient information (included in the study manual) to enable the participants to complete the ePRO on the eDevice correctly and on schedule to avoid missing or incorrect data. Prior to completing the screening assessment, the participant must complete a training module (included on the eDevice) on how to enter responses to questions on the eDevice. If a participant requires assistance entering responses in the eDevice, a caregiver or member of the study team who is trained can interview the participant and enter the participant's responses on the eDevice on the participant's behalf.

8.2.3. Antiviral Activity

For the evaluation of antiviral activity, the RSV viral load in bilateral mid-turbinate nasal swab samples will be measured at the central laboratory using an RSV qRT-PCR assay. These bilateral mid-turbinate nasal swab specimens for the determination of RSV viral load will be collected at several timepoints during the study as indicated in the Schedules of Activities. Date and time of sampling will be collected.

Bilateral mid-turbinate nasal swab samples will be collected by combining 2 swabs, one from each nostril, in the same universal transport medium tube. Only at times when sampling of both nostrils is not feasible, such as in case of bleeding in one nostril, one mid-turbinate nasal swab should be collected from one nostril (ie. the non-bleeding nostril).

One Screening sample (from upper respiratory tract collected per local SOC testing within 24 hours prior to start of Screening or bilateral mid-turbinate nasal swab as part of the study-specific Screening assessment) will be collected for the local diagnosis of RSV infection using a rapid PCR- or other molecular-based diagnostic assay. The collection of SOC sample, used for RSV diagnosis should be performed no more than 48 hours prior to randomization.

After randomization on Day 1, but immediately predose, a bilateral mid-turbinate nasal swab sample will be collected as close as possible and prior to the first administration of study intervention, aliquoted and sent to the central laboratory for:

- RSV diagnosis confirmation using a PCR-based assay
- RSV viral load

- examination for the presence of viral or bacterial co-pathogens using multiplex PCR
- viral sequencing

During the subsequent visits, as indicated in the Schedules of Activities, a bilateral mid-turbinate nasal swab sample will be collected, preferably at approximately the same time as the predose bilateral mid-turbinate nasal swab sample taken on Day 1 and preferably prior to dose administration, if applicable. This sample will be aliquoted and sent to the central laboratory for:

- RSV viral load
- viral sequencing

At Day 28, local testing for RSV detection should be performed using a rapid PCR- or other molecular-based assay on an aliquot of the study-specific bilateral mid-turbinate nasal swab sample. The bilateral mid-turbinate nasal swab sample (all remaining aliquots) will be sent to the central laboratory. A SOC upper respiratory tract sample collected at Day 28 may also be used if needed based on the local rapid PCR- or other molecular-based assay used.

In case of suspicion of the occurrence of an LRTI, an additional bilateral mid-turbinate nasal swab sample should be collected. If the collection of a bilateral mid-turbinate nasal swab sample is planned as part of the scheduled visit, collection of an additional sample in case of suspicion of LRTI is not required. This sample will be aliquoted and sent to the central laboratory for:

- RSV detection and RSV viral load
- viral sequencing

For a selected set of bilateral mid-turbinate nasal swab samples, quantitative RSV culture may be performed, if feasible, for determination of RSV infectious viral titer.

8.2.4. Health-related Quality of Life Assessment

Participants will complete the EQ-5D-5L and RiiQ Impact Scales (Appendix 10.11 and Appendix 10.9, respectively) at timepoints indicated in the Schedules of Activities to characterize the impact of RSV and its treatment on HRQOL.

8.2.5. Viral Sequencing

Development of viral resistance will be monitored by sequencing of the RSV F-gene in all baseline bilateral mid-turbinate nasal swab samples and in subsequent bilateral mid-turbinate nasal swab samples upon request of the sponsor's virologist. Other regions of the RSV genome may also be sequenced at the discretion of the sponsor's virologist. The impact of pretreatment RSV F-gene polymorphisms and relevant post-baseline F-gene changes on the antiviral response and/or clinical outcomes will be explored. Sequencing data will not be reported to the investigators. Sequencing results may be presented in a separate report.

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

8.2.6. Evaluation of RSV Viremia

Blood samples for RSV detection and quantification of RSV viral load in plasma will be collected at the time points indicated in the Schedules of Activities, to explore its role in treatment response, safety, or the status and/or course of RSV-related disease. If the collection of such a blood sample is planned as part of the scheduled visit, collection of an additional sample for suspected LRTI is not required. At the discretion of the sponsor, these samples may also be used for exploratory analysis of other pathogens in plasma that may play a role in treatment response, safety, or the status and/or course of RSV-related disease or other clinical outcomes in this population.

8.3. Safety Assessments

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

AEs

clinical laboratory tests (central)

ECG 12-lead

vital signs:

- vital signs assessments performed as part of the clinical course of RSV infection-related assessments (see Section 8.3.2: body temperature, heart rate, respiratory rate, and SpO_2)
- additional vital signs assessments: systolic blood pressure (SBP) and diastolic blood pressure (DBP)

physical examination of all body systems (at Screening) (including height and body weight measurements), directed physical examination (at visits specified in Schedules of Activities), and skin examination

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

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

Safety and tolerability will be evaluated throughout the study from signing of the ICF until the last study-related activity.

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

8.3.1. Physical Examinations

A physical examination (including height [only at Screening] and body weight measurements) and skin examination will be performed at the visits indicated in the Schedules of Activities.

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

A skin examination includes an examination of the mucous membranes, but does not include a vaginal or rectal examination. However, if the participant 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. Auscultation findings will be documented separately in the eCRF.

8.3.2. Vital Signs

Temperature (same method throughout), pulse/heart rate, respiratory rate, blood pressure, and SpO_2 will be assessed. General guidelines for measuring vital signs and SpO_2 can be found in Appendix 10.8.

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

8.3.3. Electrocardiograms

Twelve-lead ECGs will be collected at the time points specified in the Schedules of Activities and when clinically indicated or to confirm abnormal ECG findings. In case the ECG is to be taken under fasted conditions, fasted is defined as no food intake within approximately 2 hours prior to dosing and 2 hours after dosing. Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

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

For eligibility determination, the machine read ECG results, printed on the ECG device print-out of the ECG tracing, will be taken into account. If post baseline, a participant has a QTcF interval value ≥500 ms based on the machine read QTcF value, confirmation needs to be obtained as soon as possible during the same visit by another machine read ECG. If confirmed, the participant needs to be withdrawn from study intervention (see also Section 7.1) and additional ECGs need to be performed daily until resolution of the QTcF interval prolongation is confirmed (see also Section 8.4.7.2). In case other clinically relevant abnormalities are observed post baseline, a confirmatory ECG must be performed preferably within 48 hours, but no later than 72 hours, after

the results have become available. Evaluation of clinical relevance should be done on confirmed results.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Appendix 10.2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.4. Adverse Events and Serious Adverse Events

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative [LAR]) for the duration of the study.

For further details on AEs and serious adverse events (SAEs) (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 10.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, whether anticipated or not anticipated (see also Section 8.4.4), will be reported from the time a signed and dated main ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. For participants having signed a diagnostic ICF only (ie, who do not enroll in the study by signing the main ICF), reporting will be limited to AEs considered related to the sampling procedure. In case a participant is experiencing (an) ongoing AE(s) or has clinically significant laboratory or ECG abnormalities at the time of the Day 28 Follow-Up Visit, participants might be requested, at the discretion of the investigator, to have a Safety Follow-up Visit, at Day 35 and Day 49. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

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

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

8.4.2. 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 participant is the preferred method to inquire about adverse event occurrence. In addition, for the telephone visits, careful questioning should be undertaken to collect all AEs and not only SAEs.

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.4. Regulatory Reporting Requirements for Serious Adverse Events

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

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following serious AEs will be considered anticipated events:

Table 8: Anticipated Events

Pneumonia	Mucositis	Death related to clinical progression of underlying disease requiring HSCT, or graft failure
Sinusitis	Chronic Obstructive Pulmonary Disease	Sepsis/Infections (opportunistic, eg, cytomegalovirus/Epstein-Barr virus, P jiroveci, herpes zoster virus, candida, aspergillosis, viral hepatitis)
Interstitial pneumonitis	Peri-engraftment respiratory distress syndrome	Lymphadenopathy
Acute bronchitis	Idiopathic pneumonia syndrome	Neutropenia
Hypothyroidism	Bronchiolitis obliterans	Thrombocytopenia
Respiratory failure	Hepatic veno-occlusive disease	Anemia
Graft Failure	Thrombotic microangiopathy	GVHD
Osteopenia, osteoporosis, and avascular bone necrosis	Posterior subcapsular cataract	Alopecia
Bone pain	Congestive heart failure	Secondary malignancy (Secondary acute leukemias, solid tumors, and myelodysplastic syndromes)
Hemorrhagic cystitis	Bleeding	Pancytopenia
Infertility	Retinopathy, Infectious retinitis, and ocular hemorrhage	Diffuse alveolar hemorrhage

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events and/or individual anticipated serious adverse events according to the requirements of the countries in which the studies are conducted.

8.4.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 SAE and must be reported using the SAE Form (see Section 7.1).

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

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

8.4.6. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

Symptoms of RSV disease, as reported in the RiiQ, will not be reported as AEs but constitute a part of the efficacy evaluations. However, they will be reported as (S)AE if they are considered related to the study intervention or fulfill the SAE definition.

'Disease progression' should not be recorded as an AE term or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the (serious) adverse event definition (refer to Adverse Event Definitions and Classifications in Appendix 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). This pertains to both the suspected LRTI events (RSV disease progression) as well as to the progression of the underlying disease (leading to HSCT) or status of the HSCT.

8.4.7. Management of Adverse Events of Interest

Adverse event of interest for JNJ-53718678 based on nonclinical data is liver toxicity.

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

8.4.7.1. Liver Toxicity

Refer to Appendix 10.2 for protocol-required safety laboratory assessments. The severity grade of laboratory abnormalities in liver function tests (LFT) is assessed using the criteria specified in the DMID adult toxicity tables in Appendix 10.7, which is also applicable for adolescents. Refer to Appendix 10.6 for suggested actions and follow-up assessments in case of abnormal liver function in participants with normal liver function at screening. Ad hoc assessments (such as alkaline phosphatase, international normalized ratio [INR], gamma-glutamyltransferase [GGT]) may be performed at the discretion of the investigator, during unscheduled visits.

If there is suspected development of (acute) GVHD with liver involvement, monitoring and management should be per local SOC for GVHD. For participants with GVHD with involvement of the liver at enrollment, but AST/ALT <3x ULN within the 4 weeks prior to Screening, liver function should be monitored per local SOC.

If AST or ALT increases >5 x ULN and rising with or without total bilirubin increase >2 x ULN or AST or ALT remains >5 x ULN without a change in total bilirubin for more than 2 weeks, applicable for GVHD, the study intervention should be discontinued (see Section 7.1).

8.4.7.2. Cardiac Events Potentially Related to QT Prolongation

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

Additional ECG assessments are to be performed as unscheduled assessments/visits preferably 3 days after the start of coadministration with moderate or strong CYP3A4 inhibitors during the study intervention period.

A participant's study intervention must be discontinued if the participant has a confirmed QTcF interval value ≥500 ms at any scheduled visit based on the machine read QTcF value. Confirmation needs to be obtained as soon as possible during the same visit by another machine read ECG (see Section 7.1). For participants with a confirmed QTcF interval value ≥500 ms, the following measures should be taken:

- The cardiac event must be reported to the sponsor within 24 hours.
- The investigator should request urgent cardiology referral, within 24 hours if possible.
- Clinical evaluation including safety biochemistry (such as electrolytes), assessment of the use of concomitant QT prolonging drugs, and evaluation for the presence of any structural heart disease must be conducted. Levels of potassium and magnesium to be determined by the local and by the central laboratory at the timepoints specified in the Schedules of Activities.
- In case of hypokalemia and/or hypomagnesemia at screening, Day 3, Day 8, or Day 15, the levels of potassium and/or magnesium should be corrected taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required.
- An ECG should be repeated every 24 hours until resolution of QTcF interval prolongation is confirmed. The participant's condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled assessments/visits.

For participants with a laboratory abnormality of hypokalemia of <2.5 mEq/L (Grade 3) and/or hypomagnesemia of <0.9 mEq/L (Grade 3) in samples taken throughout the study intervention treatment period, the following measures should be taken (see also Section 7.1):

Repeat to confirm the results (local test), to be performed within 24 hours of the result being available at the site.

Participant's study intervention must be discontinued after confirmation of results.

Clinical evaluation including assessment of cardiovascular status and ECG must be conducted.

Electrolytes should be repeated (local laboratory) every 24 hours until resolution is confirmed. The participant's condition should be followed until resolution (return to baseline) or stabilization. During the study, these assessments will be captured as unscheduled assessments/visits.

8.4.8. Management of Complications or Sequelae of HSCT

Management of complications or sequalae of HSCT as well as the underlying disease will be at the discretion of the investigator and should follow generally accepted medical standards.

8.5. Treatment of Overdose

For this study, any dose of JNJ-53718678 greater than the total daily dose within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

8.6. Pharmacokinetics

For all participants, venous blood samples for determination of JNJ-53718678 plasma concentrations will be collected at the timepoints indicated in the Schedules of Activities (see Section 1.3.4). Samples may also be used for the analysis of metabolites of JNJ-53718678 or endogenous markers for enzymes or transporters involved in the metabolism and distribution of JNJ-53718678, at the discretion of the sponsor. Blood samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. The participant's confidentiality will be maintained.

Bioanalysis of plasma samples (applicable treatment group only [not the placebo group]) to determine plasma blood concentrations of JNJ-53718678 and, if applicable, metabolites will be performed using a validated, specific, and sensitive method by the sponsor or under the sponsor's supervision.

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

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

Other samples (eg, bilateral mid-turbinate nasal swab samples) may be analyzed for JNJ-53718678 using research or scientifically validated bioanalytical assays, at the discretion of the sponsor.

8.6.1. Substudy in Hospitalized Participants

In a rich serial PK sampling substudy, performed at selected study sites, rich serial PK blood sampling for the measurement of plasma concentrations of JNJ-53718678 will be performed in approximately 30 hospitalized participants. At selected study sites participating in the PK substudy, the ICF will contain a separate section explaining the PK substudy and separate consent can be given for this substudy.

Participants in the rich serial PK sampling substudy will undergo rich serial PK sampling at visit (dosing) Days 1 and 8, at 8 different time points within the dosing interval. The first sample should be collected before study drug intake (within 0.5 hour before). JNJ-53718678 can be taken with or without food. Samples 2 to 8 should be collected at 0.5, 1, 1.5, 2, 4, 8, and 12 or 24 hours after study drug intake. No additional sample is needed to cover the sparse PK sample to be taken during the visit at Days 1 and 8. The 12 or 24-hour PK sample must be taken before study drug intake in

the morning. If a participant is discharged prior to Day 8, the sparse PK schedule will be followed, including for Day 8 (see Table 3).

The following times need to be recorded: actual dates and times of study drug intake and actual dates and times of PK blood sampling. In addition, it should be documented whether the study intervention intake (ie, the one closest preceding the PK sample) is taken in fed state (ie, between 1 hour before and 1 hour after completion of a meal).

8.7. Pharmacokinetics/Pharmacodynamics

The PK/PD relationship of JNJ-53718678 exposure (area under the plasma concentration-time curve from time 0 to 24 hours after dosing [AUC_{24h}], maximum plasma concentration [C_{max}], or minimum plasma concentration [C_{min}]) with selected efficacy (change in viral load from baseline and clinical outcomes) and safety (including AEs and laboratory abnormalities) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships.

8.8. Genetics

Pharmacogenomics and genetics are not evaluated in this study.

8.9. Biomarkers

Blood samples will be collected for exploratory biomarker analyses (host RNA and/or proteins) at the timepoints indicated in the Schedules of Activities, on the premise that these markers may play a role in the treatment response, PK, safety of JNJ-53718678, or the status and course of RSV-related disease. Collection of the blood samples for biomarker research is mandatory, unless local regulations require these samples to be optional. In addition, leftover bilateral mid-turbinate nasal swab or blood samples may be used for biomarker analysis (eg, proteins including cytokines). Analyses of biomarkers may be conducted at the sponsor's discretion and reported separately from this study.

No human DNA analyses will be performed on these samples.

8.10. Medical Resource Utilization

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

- Assessments performed as part of the clinical course of RSV infection-related assessments (see Section 8.2.2):

  Antibiotic use for the treatment of an RSV LRTI and/or RSV-associated LRTC per the EAC's assessment after the first dose of study intervention through the last study visit.

  Requirement for, and duration of, hospital (re)admission including duration by wards level (eg, ICU) for respiratory reasons from Screening through the last study visit.

  Occurrence of GVHD or delayed engraftment.

- O_2 supplementation.
- Number and duration of medical care encounters and treatments (including physician or emergency room visits, tests and procedures, and medications, surgeries and other selected procedures; inpatient and outpatient).

For the long-term follow-up period, hospitalizations as well as data on inpatient rehabilitation, long-term care hospitalization and use of extra skilled nursing (home) will be collected. In addition, occurrence or worsening of GVHD or delayed engraftment and relapse as well as survival status will be collected.

9. STATISTICAL CONSIDERATIONS

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

The primary analysis will be performed when all randomized participants have completed the Day 49 study visit or discontinued earlier. The final analysis (for health economics purpose) will be performed when all randomized participants have completed the long-term follow-up (ie, 1 year after randomization) or discontinued earlier. Data for this analysis might be collected after database lock and unblinding for the primary analysis.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that JNJ-53718678 reduces the proportion of adult HSCT recipients with RSV URTI, who develop an RSV LRTI within 28 days after start of treatment as compared to placebo, assessed through the relative risk.

The primary hypothesis will be evaluated (in the adult cohort) in the overall population, in the population with an ALC <500 cells/µL at Screening, and in the population with an ALC <200 cells/µL at Screening. To account for this multiplicity, the theory developed by Spiessens and Debois[55] will be used, allowing all 3 tests to be performed at a pre-fixed significance level, irrespective of the outcome of the other tests. Assuming 50% of the population will have an ALC <500 cells/µL at Screening and 25% of the population will have an ALC <200 cells/µL at Screening, fixing the one-sided significance level for each of these two subgroups at 0.6%, and using an overall 2.5% one-sided significance level, the full population can be tested using 1.8% one-sided significance.

The secondary endpoints will be evaluated in the largest population (from the adult cohort) where superiority was shown on the primary endpoint.

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the ICF
Randomized	All participants who were randomized in the study
Efficacy	All participants who were randomized, treated (at least 1 dose), and had a RSV infection confirmed by central laboratory analysis, excluding participants infected with a co-pathogen (specified in Section 5.2, Exclusion Criteria) at baseline not identified during screening, analyzed as randomized
Safety	All randomized participants who took at least 1 dose of study intervention analyzed 'as treated'

9.3. Sample Size Determination

Sample size determination was performed for the adult cohort only. Assuming a progression to RSV LRTI occurring in 35% of the patients in the placebo arm, a relative risk of 40%, and a 2:1 randomization, 210 patients are needed to obtain 90% power with 2.5% one-sided significance in the primary analysis set based on a Fisher's Exact test. Assuming 15% of patients will be excluded from the primary analysis set, the total sample size becomes 249. Similar power estimates were obtained from simulations using Cochran-Mantel-Haenszel test and Fisher's Exact test.

Participants with an ALC <500 cells/µL at Screening should account for at least 50% of all participants in the adult cohort and participants with an ALC <200 cells/µL at Screening should account for at least 25% of all enrolled participants, also at the time of the interim analysis (see Section 9.2 and Section 9.4.10).

To ensure the prespecified distribution in the strata for the interim analysis, enrollment in certain lymphopenia strata (≥500 - <1,000 cells/µL or 200 - <500 cells/µL) will be temporarily paused prior to the interim analysis once sufficient patients for the interim analysis are enrolled in the corresponding stratum.

No more than 62 participants with ALC ≥500 - <1,000 cells/µL and no more than 93 patients with ALC ≥200 cells/µL can be enrolled prior to the interim analysis. Once sufficient patients have been enrolled for the interim analysis, enrollment will continue again in all strata.

Similarly, to ensure the prespecified distribution in the strata for the final analysis, enrollment in certain lymphopenia strata (≥500 - <1,000 cells/µL or 200 - <500 cells/µL) could be stopped early once sufficient patients for the final analysis are enrolled in the corresponding stratum.

No target sample size was determined for the adolescent cohort (see Section 4.2.1).

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to first patient first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The efficacy analyses will be conducted by cohort. Safety, demographic, and baseline characteristics data will be analyzed for the overall population (adult and adolescent cohorts combined).

9.4.1. Participant Information

All demographic (eg, age, height, weight, race, gender), other initial participant characteristics (physical examination, medical and surgical history, family history, concomitant diseases), RSV disease characteristics (eg, subtype, time since symptom onset), and HSCT-related characteristics (eg, donor type, cell source, GVHD history, hospitalization at screening) will be tabulated and analyzed descriptively by intervention group.

9.4.2. Efficacy Analyses

For the adolescent cohort, efficacy analysis will be limited to descriptive statistics.

For the adult cohort, primary analysis of efficacy-related endpoints will be performed in the overall population, in the population with an ALC <500 cells/μL at Screening, and in the population with an ALC <200 cells/μL at Screening, applying a multiplicity correction (see Section 9.1).

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, hierarchical testing will be applied to control for overall Type I error. The following endpoints are included in the confirmatory strategy:

1. The proportion of participants who develop RSV LRTI per the EAC's assessment (see Section 9.6) through Visit Day 28, ie, primary endpoint;
2. The proportion of participants who develop an RSV-associated LRTC per the EAC's assessment (see Section 9.6) through Visit Day 28;
3. Time to resolution of symptoms, assessed through an instrument for patient-reported symptoms (RiiQ Symptom Scale);
4. Number of supplemental O_2 free days through Day 28;
5. Proportion of participants hospitalized (of participants who were not hospitalized at baseline);
6. The proportion of participants progressing to respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) and/or death (all-cause mortality);
7. Total length of hospital stay (time in hospital before first dosing is discarded);

First, the primary endpoint will be tested for superiority at the 1-sided 2.5% significance level. If superiority is shown on the primary endpoint, the first secondary endpoint in the sequence as indicated above will be tested for superiority at the same significance level. If superiority is shown for this secondary endpoint, further secondary endpoints will be tested for superiority in the sequence as indicated above, and at the same significance level. In case superiority is not shown for an endpoint, no further endpoints in the sequence will be tested for superiority.

9.4.2.1. Primary Endpoint: Development of RSV Lower Respiratory Tract Infection

The proportion of participants who develop an EAC-confirmed RSV LRTI through Visit Day 28 will be analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

9.4.2.2. Key Secondary Endpoints

For the hypothesis testing, the following methods will be used:

- Time to resolution of symptoms will be analyzed using a stratified Gehan-Wilcoxon test (using the randomization stratification factors).
- Total length of hospital stay and the number of supplemental O_2 free days will be analyzed using a Hodges-Lehmann test.
- For the proportion of participants hospitalized, and the proportion of participants progressing to respiratory failure and/or death, a Cochran-Mantel-Haenszel test stratified by the randomization stratification factors, will be used as for the primary analysis.

9.4.2.3. Clinical Course of RSV Infection

Endpoints related to evaluation of the clinical course of RSV infection will be analyzed graphically and descriptively. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented.

Time to-variables (eg, time to resolution of symptoms) will be analyzed using Kaplan-Meier plots and will be modeled using an accelerated failure time model, adjusted for the randomization stratification factors, to estimate differences between intervention groups.

Results from the RiiQ Impact Scale and PGI (PGI-S, PGI-C, and PGI-H) assessments will be descriptively summarized by intervention group.

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

9.4.2.4. Antiviral Activity

Antiviral activity will be determined based on measurements of RSV viral load in bilateral mid-turbinate nasal swab samples by a qRT-PCR assay. These data will be analyzed graphically and descriptively as described in the SAP. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated. For categorical variables, frequency tables will be presented. Kaplan-Meier Curves will be produced to graphically describe the time to event data.

Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of intervention, strata, visit, and intervention-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within subject errors over time. The Kenward-Roger method will be used to approximate the degrees of freedom. Differences between intervention groups in viral load, and the difference in the AUCs between intervention groups will be derived using appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals.

9.4.2.5. Health-related Quality of Life Assessment

Results from the HRQOL assessment (through EQ-5D-5L and RiiQ Impact Scales) will be descriptively summarized by intervention group.

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

9.4.2.6. Correlation Between Antiviral Effect and Clinical Course Endpoints

Selected antiviral effect and selected clinical course endpoints (primary and key secondary endpoints) will be subjected to correlation analysis and will be presented in a tabular and/or graphical display.

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

9.4.2.7. Viral Sequencing

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

9.4.3. Safety Analyses

Safety data will be presented descriptively. For safety, baseline is defined as the last assessment prior to the first intake of study intervention.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Intervention-emergent AEs are AEs with onset during the intervention 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 participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, who experience a severe AE (ie, at least Grade 3) or a SAE, or who experience anticipated events.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. The laboratory abnormalities will be determined per the criteria specified in the DMID Adult (see Attachment 10.7, also for adolescents) and in accordance with the normal ranges of the clinical laboratory if no gradings were available.

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

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

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

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

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values.

The 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 according to Fridericia's formula.[5,28,33,47]

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

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

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

Vital Signs

Descriptive statistics of blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point (see also Section 8.2.2). The percentage of participants with markedly abnormal results (specified in the SAP) will be summarized.

9.4.4. Pharmacokinetic Analyses

The PK samples taken from all participants in the study (see Section 1.3.4.1), as well as the rich serial PK samples collected in the PK substudy (Section 1.3.4.2) will be used for popPK model development and/or popPK model update. The PK samples taken from participants in the rich serial PK substudy will be analyzed as specified in Section 9.4.4.1. PopPK analysis of plasma concentration-time data of JNJ-53718678 from all participants (including those of rich PK substudy, see Section 9.4.4.1 for details) will be performed using (non)-linear mixed-effects modeling. Population PK modeling will be used to describe the concentration-time profiles and estimate the exposure parameters (AUC_{24h}, C_{trough}, and C_{max}) of JNJ-53718678. Available baseline subject characteristics (demographics, body weight, laboratory variables, genotype, etc.) may be explored as potential covariates affecting PK parameters of JNJ-53718678. Details will be given in a popPK analysis plan and the results of the popPK analysis will be presented in a separate popPK report.

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

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

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

9.4.4.1. Substudy in Hospitalized Participants

For the intensive PK samples of the rich PK substudy, non-compartmental PK analysis of JNJ-53718678 will be performed using actual sampling time and plasma concentrations obtained from rich serial PK blood sampling for approximately 30 participants. Descriptive statistics will be provided for the PK parameters (C_{trough}, C_{max}, t_{max}, C_{min}, and AUC_{24h}) derived, including graphical analyses of the data. Results will be presented in a separate PK report.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of JNJ-53718678 population-derived exposure parameters with selected antiviral activity parameters, clinical outcomes, and safety endpoints will be explored. In case there is a relationship, this will be characterized using (non)-linear mixed effect models. These relationships will be presented in a tabular and/or graphical display.

9.4.6. Biomarkers Analyses

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

9.4.7. Medical Resource Utilization

Medical resource utilization will be descriptively summarized by intervention group.

9.4.8. Other Analyses

Data on viral (other than RSV) or bacterial pathogens (both by multiplex PCR) determined in bilateral mid-turbinate nasal swab samples collected at Day 1 predose (or Screening) will be listed and tabulated.

9.4.9. Health Economics

A separate analysis for health economics purpose will be performed after completion of the long-term follow-up. Data on survival status, morbidity and hospitalizations/MRU will be descriptively summarized per intervention group.

9.4.10. Interim Analysis

One interim analysis is planned when approximately 50% of the planned participants from the adult cohort have completed the Day 28 assessments (or discontinued earlier). At the time of the interim analysis, participants with an ALC <500 cells/µL at Screening should account for at least 50% of all enrolled participants, and participants with an ALC <200 cells/µL at Screening should account for at least 25% of all enrolled participants. This interim analysis will include safety, testing for futility, early superiority, and an unblinded sample size re-estimation. During the interim analysis, enrollment will continue.

Interim testing for futility will focus on the full population only, using the Go-NoGo framework.[23] Interim testing for early superiority will focus on the full population only, using a 0.001% one-sided significance level.

The unblinded sample size re-estimation will use the observed RSV LRTI rates in the full population and calculate the required sample size for the adult cohort to obtain 90% power for the final analysis. This calculated value will be increased based on the proportion of patients in the efficacy analysis set as observed at interim. The study sample size for the adult cohort will not be decreased, and not be increased to beyond 375 patients. The new sample size will not be communicated to the sponsor nor the investigators.

Details on the testing for futility, early superiority, and sample re-estimation will be provided in the SAP and/or IDMC Charter.

During and after this interim analysis, investigators, participant(s), and sponsor representatives will remain blinded. An IDMC (see Section 9.5) will monitor and review the results from the interim analysis in an unblinded manner. A Sponsor Committee, consisting of senior sponsor personnel not involved in the conduct of the study, will be established and will be responsible for decision making, considering the IDMC recommendation, and will communicate these decisions to the study team. Details are provided in the IDMC Charter. During the interim analysis, the Sponsor Committee will remain blinded.

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

9.5. Independent Data Monitoring Committee

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

meet periodically to review safety data and results from the interim analysis. After the review, the IDMC will provide recommendations to the Sponsor Committee, who will be responsible for decision making, considering the IDMC recommendation, and who will communicate these decisions to the study team. Details are provided in the IDMC Charter.

Additionally, given the longer dosing duration of JNJ-53718678 used in this study and the population targeted, the IDMC will perform the first unblinded safety review prior to (should a safety signal warrant) or after the 18th patient has completed the Day 28 assessments (or discontinued earlier).

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

9.6. Endpoint Adjudication Committee

An external blinded EAC will review clinical data (see Section 8.2.1.5 for details) to determine whether an RSV LRTI and/or RSV-associated LRTC has developed (as defined in Section 3). The clinical data will be used to determine if the event meets the criteria for any of the categories defined in Section 3 and excludes other potential causes such as pulmonary embolism, cardiogenic shock, heart failure, and fluid overload. The EAC advice will be stored electronically.

Additional information will be available in the EAC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	Adverse event
ALC	Absolute lymphocyte count
AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}24h}$	AUC from time of administration up to 24 hours post dosing
$AUC_{0\text{-}\infty}$	AUC from time of administration extrapolated to infinity
BAL	Bronchoalveolar lavage
BCRP	breast cancer resistance protein
bid	twice daily
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
CT	computed tomography
C_{trough}	Predose plasma concentration
CYP	Cytochrome P450
DIDB	Drug Interaction Database
DM	diabetes mellitus
DMID	Division Of Microbiology And Infectious Diseases
DNA	deoxyribonucleic acid
DTP	direct-to-patient
EAC	Endpoint Adjudication Committee
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EOI	end of intervention
EQ-5D-5L	5-level EuroQol 5-Dimension Questionnaire
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GHVD	graft versus host disease
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HSCT	Hematopoietic stem cell transplant
ICF	informed consent form

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
IC	immunocompromised
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobin M
INR	international normalized ratio
IPPI	Investigational Product Preparation Instruction
IRB	Institutional Review Board
IS	immunosuppressants
IVIG	Intravenous immunoglobulin
IWRS	interactive web response system
LAR	Legally acceptable representative
LRTC	Lower respiratory tract complication
LRTI	Lower respiratory tract infection
LT/LFT	liver tests/liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MRCP	magnetic resonance cholaniopancreatography
MRI	magnetic resonance imaging
MRU	medical resource utilization
NSAID	non-steroidal anti-inflammatory drugs
OATP	organic-anion-transporting polypeptide
OCT	organic cation transporter
OTC	over the counter
$paEC_{90}$	protein-adjusted 90% effective concentration
PBPK	physiologically-based pharmacokinetic(s)
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PGI-H	Patient Global Impression of Health
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PT	prothrombin time
PTT	partial thromboplastin time
qd	Once daily
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcI	individual-corrected QTc
QTcF	QT interval corrected using Fridericia's formula
q12h	every 12 hours
q24h	every 24 hours
RiiQ	Respiratory Infection Intensity and Impact Questionnaire
RNA	ribonucleic acid
RSV	Respiratory syncytial virus
rtv	ritonavir
SAE	Serious adverse event
SD	Standard deviation
SoA	Schedule of Activities
SOC	Standard of care
SUSAR	suspected unexpected serious adverse reaction
Tbili	total bilirubin
TEAE	treatment-emergent AE

TIBC	total iron binding capacity
TR	tissue radioactivity
TQT	thorough QT
ULN	upper limit of normal
WBC	white blood count

Definitions of Terms [if applicable]

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume Mean Corpuscular Hemoglobin (MHC) MHC concentration % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A 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.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Cholesterol (total, HDL, and LDL) Triglycerides (TG)	Urea Total bilirubin (direct and indirect) Alkaline phosphatase Uric acid Creatinine Calcium Phosphorus Magnesium Glucose (preferentially fasting) $eGFR_{crea}$	
	Note: $eGFR_{crea}$ to be calculated per CKD-EPI.[38] The levels of potassium and magnesium are determined by the local and by the central laboratory at the timepoints specified in the Schedules of Activities. In case of hypokalemia and/or hypomagnesemia at screening, Day 3, Day 8, or Day 15, the levels of potassium and/or magnesium should be corrected taking into account any underlying condition and as soon as possible to prevent cardiac disturbances. Appropriate clinical management per local SOC (including but not limited to checking the corrected values at the local laboratory) may be required. See also Section 8.4.7.2 for cardiac safety measures.		
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment[a] (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria	
	a. At central lab		

	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.
Pregnancy	Serum (only at Screening) and urine pregnancy testing for all woman.

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior 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 participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

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

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

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

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

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

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

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

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.6, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.6.

INFORMED CONSENT/ASSENT PROCESS

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

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

The participant 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/assent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

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

Written assent should be obtained from participants who are able to write. A separate assent form written in language the participant can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form will be given to the participant, and to the participant's parent(s) or if applicable LAR.

Minor patients reaching the age of majority (per local regulatory requirements) during the study will be required to sign an ICF.

DATA PROTECTION

Privacy of Personal Data

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

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

The informed consent/assent obtained from the participant includes explicit consent/assent 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/assent also addresses the transfer of the data to other entities and to other countries.

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

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and

confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research (refer to Section 7.2, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

An IDMC and EAC will be established as indicated in Section 9.5 and Section 9.6, respectively.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-53718678 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including 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/assent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-53718678, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

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

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the

investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

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

If necessary, queries will be generated in the 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.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent/assent; 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; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention 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 pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries
- Chest X-ray and local radiologist's or investigator's interpretation

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

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring 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). 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.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

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

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

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

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

Study Termination

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

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

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

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

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. 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 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 main ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording). For participants having signed a diagnostic ICF only (ie, who do not enroll in the study by signing the main ICF), reporting will be limited to AEs considered related to the sampling procedure.

Serious Adverse Event

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

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

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

Note: Abnormalities in liver function tests (see Appendix 10.2) are considered as medically important. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 10.6 Liver Safety. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR*) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as a SAE. See also Section 8.4.

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 and any Addenda.[34]

Adverse Event Associated With the Use of the Intervention

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

ATTRIBUTION DEFINITIONS

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

SEVERITY CRITERIA

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

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

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

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

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

For more details, refer to the DMID severity grading scale (see Appendix 10.7).

SPECIAL REPORTING SITUATIONS

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

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

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

PROCEDURES

All Adverse Events

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

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

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number

- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a 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.

Disease progression should not be recorded as an AE term or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition. Follow-up will end at Day 49; there is no longer term follow-up planned.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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

Procedures

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

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.5, Pregnancy and Appendix 10.4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **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. A high follicle stimulating hormone (FSH) 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 (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- **sterile due to pretransplant conditioning protocols**

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

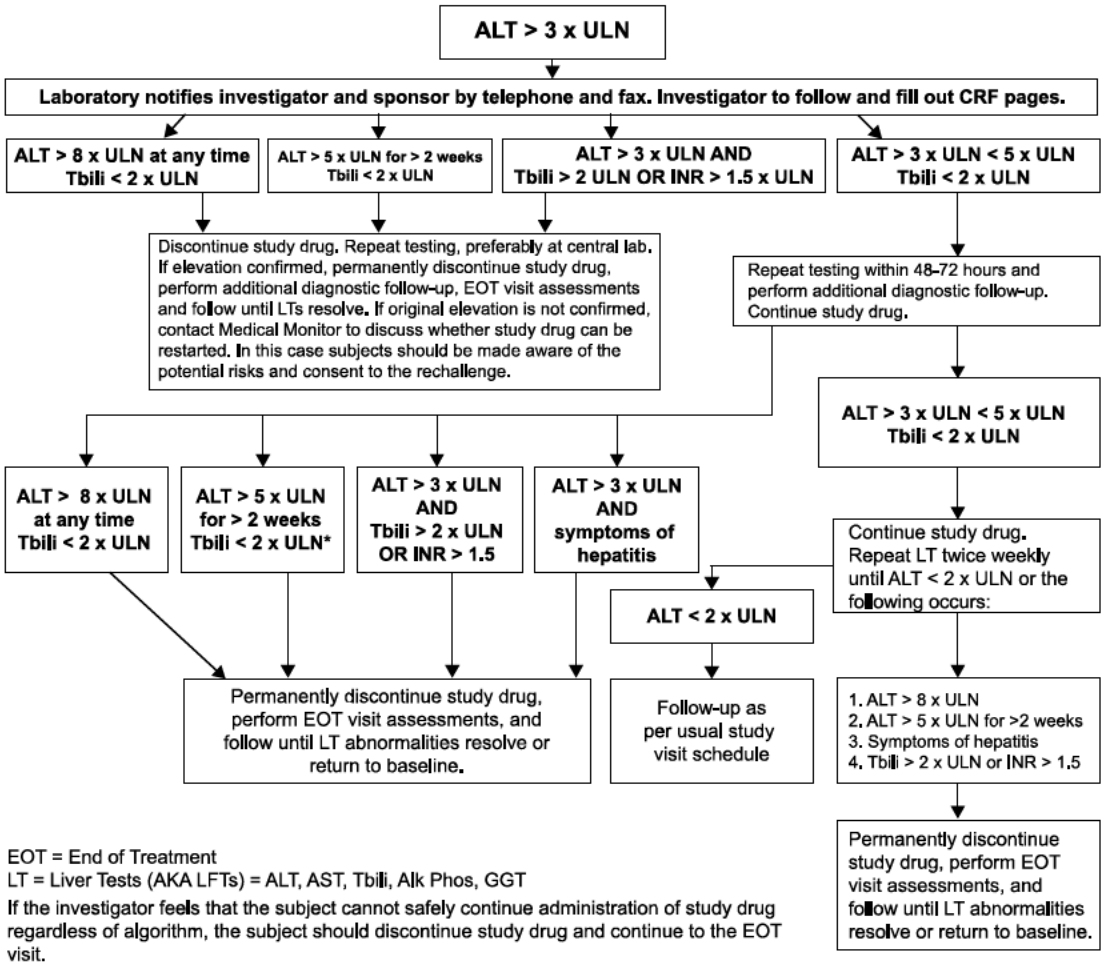
Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER-INDEPENDENT **Highly Effective Methods That Are User-Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)

• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion/ligation without reversal operation
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Guideline Algorithm for Assessment and Management of Abnormal Liver Tests in Subjects without Underlying Liver Disease



EOT = End of Treatment
LT = Liver Tests (AKA LFTs) = ALT, AST, Tbili, Alk Phos, GGT

If the investigator feels that the subject cannot safely continue administration of study drug regardless of algorithm, the subject should discontinue study drug and continue to the EOT visit.

This algorithm has been developed assuming normal liver function at baseline. For subjects with pre-existing liver disease or LT abnormalities as baseline, clinical teams are encouraged to consult the Hepatic Safety Group.

*Cases meeting these criteria in the absence of initial findings of cholestasis, (i.e., ALP < 2 x ULN) must be promptly reported to the company using the Serious Adverse Event Form and also recorded in the designated CRF supplemental Liver Safety Report Form.

The following definitions of patterns of Drug Induced Liver Injury (DILI) are used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos*/ULN)
Hepatocellular	**ALT ≥ 3 × ULN**	**≥ 5**
Cholestatic	**ALT ≥ 3 × ULN**	**≤ 2**
Mixed	**ALT ≥ 3 × ULN and AP ≥ 2 × ULN**	**> 2 to < 5**

Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, BMI. Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, or lymphadenopathy. Assess for history of prior abnormal liver tests or liver disease, including viral hepatitis, obesity, metabolic syndrome, CHF, occupational exposure to hepatotoxins, diabetes, gallstone disease or family history of gallstone, or liver disease. Specifically record history of alcohol use, other medications including acetaminophen, NSAID's, OTC herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A or hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in eCRF for other relevant H&P information. In the above algorithm, symptoms of hepatitis include fatigue, nausea and vomiting, RUQ pain/tenderness, fever, rash, or eosinophils > 5% on WBC differential.

Imaging is strongly recommended to exclude other liver injury causes, particularly if Tbili or ALP is >2xULN, or when clinically indicated based on medical history (e.g. to exclude NASH). Imaging is mandatory if participant meets criteria for study drug discontinuation according to the algorithm above. Liver ultrasound is the recommended initial imaging modality with consideration of further imaging (e.g. CT, MRI, MRCP, ERCP, Doppler studies of hepatic vessels, etc.), if indicated based on ultrasound findings or clinical situation.

If Tbili is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. CBC with WBC and eosinophil count platelet count, INR, and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, PT and PTT should be obtained and these values should be followed until normal, along with

documentation of whether parenteral vitamin K was given, along with the effect of such treatment on INR.

If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-HAV IgM, anti-HAV total, HBsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, anti-HEV IgM (even if the participant has not traveled to an endemic area for hepatitis E), EBV, and CMV screen.

a. If participant is immunosuppressed, test for HCV RNA and HEV RNA by PCR
b. If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in participants who are immunosuppressed.
c. If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

Assuming that the history, physical, and initial imaging and laboratory have not revealed a cause of elevated LTs, screen for other causes of liver disease including: total protein and albumin (estimate globulin fraction and do quantitative immunoglobulins if elevated), ANA, anti-LKM1 (anti liver-kidney microsomal antibodies), ASMA (anti-smooth muscle antibodies), ESR, and CRP. If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then GGT, AMA (anti-mitochondrial antibody) and pANCA (anti-neutrophil cytoplasmic antibody) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study drug in the clinical trial or making the participant more susceptible to DILI, test iron/TIBC and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If participant is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If participant is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.

A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated. A liver biopsy may be considered:

a. If there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
b. If peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak AlkP has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
c. In cases of DILI where continued use or re-exposure to the implicated agent is expected.
d. If liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

If pertinent, copies of hospital discharge summary, radiology, pathology, and autopsy reports should be obtained.

10.7. Appendix 7: Toxicity Tables

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE[42] – 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 dysrhythmia; 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 fluid 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

10.8. Appendix 8: General Guidelines for Measuring Vital Signs and SpO_2

Variability in the measurement of vital signs and SpO_2 is to be expected due to a number of reasons; therefore, general guidelines for measuring vital signs and SpO_2 have been developed to have a more consistent approach across sites and countries related to the methodology for measuring these clinical parameters. General instructions are provided in Section 2 for both inpatient and outpatient level of care.

Parameter	General Instructions
Blood Pressure	• While participant is hospitalized, if possible, use the same blood pressure measurement methodology for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. In the sitting position, the participant should be comfortably seated, with the legs uncrossed. When measurements are taken in the supine position, the arm should be supported with a pillow. • Blood pressure measurements should preferentially be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. • If an automated device is not available, a properly maintained mercury sphygmomanometer is preferred over aneroid and hybrid sphygmomanometers. When using a mercury sphygmomanometer, the mercury column should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mm Hg. • Preferentially, the standard location for blood pressure measurement is the upper arm, with the stethoscope at the elbow crease over the brachial artery (with manual technique). Clothing that covers the arm should be removed prior to the placement of the cuff.
Heart Rate	• While participant is hospitalized, if possible, use the same heart rate measurement methodology for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Heart rate measurements should preferentially be assessed with a completely automated device. • Manual techniques will be used only if an automated device is not available. • If manual measurement, auscultation of the heart or pulse (radial, brachial) determination are considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) count are considered acceptable.
Respiratory Rate	• While participant is hospitalized, if possible, use the same respiratory rate measurement methodology for all patients enrolled at the site.

	• Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Respiratory rate measurements can be assessed with an automated device or with manual measurement (no preference). • If manual measurement is used, inspection (preferred) or auscultation of the lungs (alternative) are considered acceptable. • If manual measurement, 30 seconds (minimum) or 1 minute (preferred) count are considered acceptable.
Temperature	• While participant is hospitalized, if possible, use the same type of temperature measurement methodology for all participants enrolled at the site. • Electronic devices (tympanic, oral) are preferred over traditional mercury thermometers (for oral temperature). • Tympanic (preferred) or oral (alternative) temperature measurements are considered acceptable. Axillary temperature should be avoided since it provides the worst estimate of core temperature and it is largely influenced by environmental conditions.
SpO_2	• While participant is hospitalized, if possible, use the same type of probe for all patients enrolled at the site. • Prior to the measurement, participant needs to be rested for at least 5 minutes, and preferably 10 minutes in a quiet setting without distractions. • Participant can be in either a sitting or supine position. • Pulse oximetry measurements using finger, toe, earlobe or frontal sensors are considered acceptable. If using the digits, assess for warmth and capillary refill, since adequate arterial pulse strength is necessary for obtaining accurate SpO_2 measurements. • Avoid placing the sensor on sites distal to indwelling arterial catheters, blood pressure cuffs, or venous engorgement (eg, arteriovenous fistulas, blood transfusions). • For hospitalized participants receiving supplemental O_2, the measurement should be performed after 5 minutes on room air. • If it is determined by the investigator that it is unsafe to remove the participant's supplemental O_2 for assessment of O_2 saturation (eg, participant is on high-flow mask), then it should be recorded in the source documentation as not assessed and the reason should be documented.

10.9. Appendix 9: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)

10.9.1. Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)[a] Symptom Scale

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

1. During the past 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] Influenza intensity and impact questionnaire (Flu iiQ™) ©RH Osborne (2006). No part of the Flu iiQ™ may be copied or reproduced in any form without written permission from the authors: measuredsolutions@bigpond.com
(English administration once daily)
Adapted with permission of RH Osborne.

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

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

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

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

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

[a] Influenza intensity and impact questionnaire (Flu iiQ™) ©RH Osborne (2006). No part of the Flu iiQ™ may be copied or reproduced in any form without written permission from the authors: measuredsolutions@bigpond.com
(English administration once daily)
Adapted with permission of RH Osborne.

4. During the past 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	☐	☐	☐	☐

10.10. Appendix 10: Patient Global Impression [PGI] Scales

Patient Global Impression of Severity (PGIS) for RSV studies

Overall, how severe were your respiratory infection symptoms today?

a. No respiratory infection symptoms today
b. Mild
c. Moderate
d. Severe
e. Very Severe

Patient Global Impression of Change (PGIC) for RSV studies

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

Patient Global Impression of Health (PGIH) for RSV studies

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

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

10.11. Appendix 11: 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

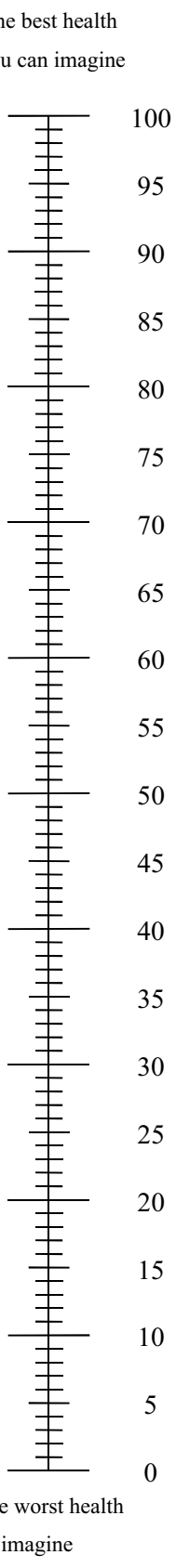
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 <u>best</u> health you can imagine.
  0 means the <u>worst</u> 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 ☐



10.12. Appendix 12: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor will be providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants (or their caregivers for adolescents) will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants or their caregivers will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participants or their caregivers and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19 during the treatment period and in case the participant's safety is considered to be at risk, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Additional follow-up and management of laboratory-confirmed SARS-CoV-2 infections, diagnosed during the study, in participants will be per local standard of care, independent from the study visits. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Missed assessments will be captured in the clinical trial management system as protocol deviations (applicable only for Data Managers and the site monitors).

Missed visits, out-of-window visits, and missing assessments will be labelled with the prefix "COVID-19-related" in the eCRF/eSource by the site personnel where needed.

If a participant is unable to travel to the study site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the study monitor and may be considered to ensure continuity of treatment, upon sponsor's approval:

- A caregiver or family member may pick up study intervention on behalf of the participant if first discussed and agreed by the participant. The conversation with the participant must be documented in the participant source documents. The participant must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, to provide guidance for study intervention transportation as per dosing instructions, and to maintain participants' privacy. Identification of who will pick up the study intervention must be confirmed and documented in the participant's source documents.
- Investigative or home health site staff may deliver study intervention directly to the participant's home. Compliance with the guidance for study intervention transportation as per dosing instructions and transit conditions must be clearly documented within the participant source documents.
- If no other alternative is feasible, direct-to-patient (DTP) shipment of study intervention from the site may be considered with prior approval from the sponsor. Site staff need to obtain participant's permission and record this in the participant source documents for direct-to-patient shipments. It is important to note this process may not be allowed by the health authorities and a specific approval process must be followed with the sponsor before moving forward. If requested by the site, the sponsor will investigate local requirements and confirm health authority requirements for DTP shipment. If approval is granted by the sponsor, specific procedures including shipment conditions, preferred courier services, and documentation requirements will be communicated by the sponsor to the site.
- The date and time of the study intervention administration at the participant's home at Day 1 instead of at the study site will be documented in the participant's source documents and in the eCRF.

If a participant cannot visit the study site in person at Day 1, the sponsor recommends that any study assessment that may be captured as home visit [such as but not limited to ECG, bilateral mid-turbinate nasal swab, RiiQ Symptom Scale, PGI-S/PGI-H, RiiQ Impact Scales, EQ-5D-5L, clinical evaluation of the course of RSV, chest imaging, LRT sampling] for that particular visit be collected. These assessments and collection should be performed at participant's home by trained delegated site staff or home health service staff.

If required, bilateral mid-turbinate nasal swab, LRT sampling and blood samples for RSV viremia can be stored and picked up by site staff or courier. If possible, central laboratory testing as outlined

in the protocol is to be continued. If central laboratory tests cannot be performed, the use of a local laboratory is allowed for study-related analyses. A copy of the local laboratory report should be reviewed by the investigator and retained, along with reference ranges, for source documentation and captured in the eCRF. RSV viremia is sent to central lab only. If imaging is required according to the current Schedule of Activities and cannot be performed at the site due to COVID-19 related restrictions, the use of local facilities close to the participant's home is permitted provided these facilities can adhere to the protocol requirements, but provision of scans to the investigative site and central readers should be arranged by the investigator and documented. If imaging is not possible as outlined in the Schedule of Activities, missed imaging should be documented as a deviation related to COVID-19 and be done as soon as possible.

There are some assessments that could be conducted virtually via telephone (or videoconference, eg, Facetime, Skype, if possible) with participants and/or caregivers in their homes, if allowed by local regulations. These virtual assessments include review of AEs and concomitant medications. Collection of medical records associated with the diagnosis of RSV LRT and recording of immunosuppressants exposures as applicable should continue. Please note, the visit windows included in the Schedule of Activities are still applicable. It must be documented in the eCRF if a visit occurs virtually due to COVID-19.

In case home visits cannot be performed then such study assessments that can be performed virtually are accepted.

The study assessments that require investigator judgement should be conducted by a medically qualified site or home health staff member identified on the site delegation log.

On-site monitoring visits may not be possible due to local regulations, restrictions and guidance. In these cases, the Site Manager will conduct site monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in future to catch up on source data verification. Remote source data verification of electronic records might be performed if possible and if allowed by local/national regulations, restrictions and guidance.

During the COVID-19 pandemic and at the impacted sites, clinical Site GCP Audits with direct impact/engagement from the clinical investigator team would be not conducted to comply with national, local and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

For subjects ≥13 and <18 years of age, when, per local procedures, both caregivers need to provide consent, the sponsor allows obtaining the second consent remotely (phone or video) if allowed per local guidance.

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT

There are no available data suggesting additional risk to participants in JNJ-53718678 clinical studies caused by locally approved (and including emergency use-authorized) COVID-19 vaccines or an interaction between COVID-19 vaccines and JNJ-53718678.

Local package inserts for COVID-19 vaccines, including contra-indications, must be followed as well as local vaccination guidelines.

For participants with signs and symptoms of febrile illness or acute infection, it is recommended that administration of COVID-19 vaccines be timed to occur after study completion or at least 1 week after the last dose of study intervention. Investigator discretion and overall assessment of clinical stability will be relied on if there is a medical need to administer vaccine during the study period.

Investigators should make an assessment of the relatedness of any AE reported following COVID-19 vaccination to study intervention, the underlying RSV infection, the underlying disease (leading to HSCT), and/or COVID-19 vaccine (as described in Section 10.4). If the event is serious and considered related to both the COVID-19 vaccine and the study intervention, it is to be recorded as a serious adverse reaction (as described in Sections 8.4. and 10.4). Adverse Events Expectedness is described in Sections 8.4. and 10.4.

In case a participant received COVID-19 vaccine during study period, the COVID-19 vaccine must be documented on the concomitant therapy page of the eCRF (see Section 6.6).

10.13. Appendix 13: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	7 May 2021
Amendment 5	03-Aug-2020
Amendment 4	10-July-2020
Amendment 3	03-June-2020
Amendment 2	11-Dec-2019
Amendment 1	21-Jun-2019
Original Protocol	7-Jun-2019

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

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 study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	07-May-2021 13:14:59 (GMT)	Document Approval