Janssen Research & Development

Statistical Analysis Plan

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

JNJ-53718678 (rilematovir)

Status: Approved
Date: 28 December 2021
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.: EDMS-ERI-197113532, 1.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	28DEC2021	Not Applicable	Initial release

1. INTRODUCTION

On 28-Oct-2021, the Sponsor decided to terminate the FREESIA study (53718678RSV2005) early due to the low enrollment. The 2 ongoing participants were allowed to complete the study till study Day 49. Although a stable version of the Statistical Analysis Plan (SAP) of the study was ready to be endorsed (available in RIMdocs EDMS-ERI-197113532 V0.21), it was decided to simplify and to reduce the statistical outputs to individual patient profile because data of only 3 randomized participants were collected. Therefore, no summary statistics across participants will be produced, and data will be reported as a listing generated for each participant (patient profile).

This SAP contains identification of variables that will be included in patient profile and reported for the clinical study report (CSR), and definitions of derived variables for the FREESIA study. The SAP is to be interpreted in conjunction with the protocol.

This SAP covers the primary analysis. The primary analysis will be performed when all randomized participants have completed the Day 49 study visit or discontinued earlier. Participants will not continue through the long-term follow-up (LTFU) and so, the final analysis (for health economics purpose) will not be performed.

Due to the small number of participants no pharmacokinetic (PK) or pharmacokinetic/pharmacodynamics (PK/PD) analysis will be performed, and only observed plasma levels of rilematovir will be reported in the CSR.

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

1.1. Trial Objectives

Given the small number of enrolled participants, no analyses will be performed to evaluate the study objectives listed in Table 2. Only individual patient profiles will be provided.

Table 2: Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of JNJ53718678 on the development of RSV Lower Respiratory Tract Infections (LRTIs) in adult hematopoietic stem cell (HSCT) recipients with RSV Upper Respiratory Tract Infections (URTI).	The proportion of participants who develop RSV LRTI (see definition below Table 2) 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 Complication (LRTC) in adult and adolescent HSCT recipients with RSV URTI.	The proportion of participants who develop RSV-associated LRTC (see definition below Table 2) per the EAC's assessment through Visit Day 28.
To evaluate the safety and tolerability of JNJ-53718678	Safety and tolerability, as assessed by adverse events (AE), clinical laboratory testing, electrocardiograms (ECGs), vital signs, throughout the study

Table 2: Objectives and endpoints

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 • 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/pulse 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

Table 2: Objectives and endpoints

Objectives	Endpoints
	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 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) • 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

Table 2: Objectives and endpoints

Objectives	Endpoints
	• 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)
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: • medical resource utilization • RSV viral subtype and presence of pretreatment RSV F-gene genetic variations • 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

Definition

RSV LRTI is 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 is 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 (e.g., 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

Due to the small numbers of participants enrolled, no endpoint adjudication will be performed by the EAC.

1.2. Trial 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 rilematovir in adult (ie, adult cohort) and adolescent (ie, adolescent cohort) HSCT recipients with an RSV URTI.

Participants are enrolled in either the adult or adolescent cohort:

- Adult cohort: adult participants ≥18 to ≤75 years of age.

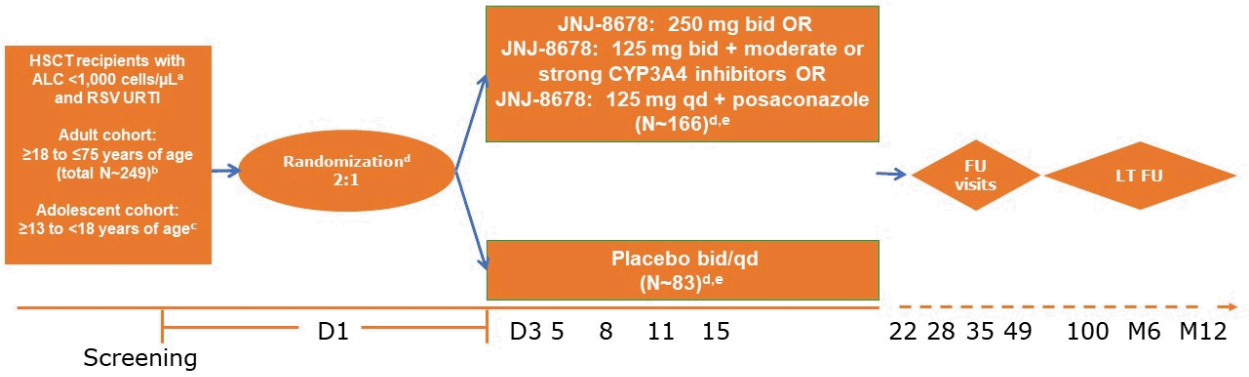
- Adolescent cohort: adolescent participants ≥13 to <18 years of age.

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

The study includes a Screening Period (Day -2 to Day 1), a Treatment Period (Day 1 to Day 21), a Follow-up Period (Day 22 to Day 49) and a long-term follow-up period (Day 50 to one year). On Day 49, participants complete the study follow-up and continue to LTFU for one year. The total study duration for each participant is approximately 365 days (Screening included). Due to study early termination, participants will not continue through the LTFU and data will be collected through Day 49 only.

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

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.

For more information on the trial design, see Section 4 *Study Design* of the study protocol.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that rilematovir 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 by the relative risk.

The primary hypothesis will be evaluated (in the adult cohort) in the overall population, in the population with an Absolute lymphocyte count (ALC) <500 cells/µL at Screening, and in the population with an ALC <200 cells/µL at Screening, respectively. To account for this multiplicity, the theory developed by Spiessens and Debois (Spiessens 2010) 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.

Hierarchical testing of the secondary endpoints will be performed in the largest population only (from the adult cohort) where superiority was shown on the primary endpoint.

No statistical hypothesis testing will be performed in the adolescent cohort.

1.4. Sample Size Justification

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. The sample size computation is based on an exact procedure (Fisher's Exact test), which is commonly used when sample sizes are small and expected event frequencies low. However, the primary endpoint will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test which takes into account the randomization stratification factors in the analysis. Similar power estimates were obtained from simulations using the CMH test and the 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 (IA).

To ensure the prespecified distribution in the strata for the IA, enrollment in certain lymphopenia strata (≥500 - <1,000 cells/μL or 200 - <500 cells/μL) will be temporarily paused prior to the IA once sufficient patients for the IA 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 IA. Once sufficient patients have been enrolled for the IA, enrollment will continue again in all strata.

Similarly, to ensure the prespecified distribution in the strata for the primary 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 primary analysis are enrolled in the corresponding stratum.

No target sample size was determined for the adolescent cohort

1.5. Randomization and Blinding

Randomization

Central randomization will be implemented in this study using an interactive web response system (IWRS). 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 (ALC categories: <200

cells/µL, 200 - <500 cells/µL, and ≥500 - <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.

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, after database lock for the IA, 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 IA.

The IA will be implemented through an Independent Data Monitoring Committee (IDMC), providing recommendations to a Sponsor Committee. Only the IDMC and the independent Statistical Support Group will be unblinded to the data. Details are specified in the IDMC charter.

2. GENERAL ANALYSIS DEFINITIONS

Clinical data will be reported through patient profiles, which will be produced using SAS® version 9.4 (or higher).

2.1. Visit Windows and Phase Definitions

2.1.1. Phase Definitions

Not applicable

2.1.2. Baseline

Not applicable

2.1.3. Relative Day

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

The relative day (reldy) will be defined as:

reldy=visit date – reference date + 1 for visits on or after Day 1,

reldy=visit date – reference date for visits before Day 1.

Consequently, there is no ‘Day 0’ defined.

2.1.4. Analysis Windows for Analysis Visits and Time Points

All values collected for the parameters listed below will be considered based on their actual date and time.

2.2. Analysis Sets

2.2.1. All Randomized Analysis Set

Patient profiles will be produced for all participants who signed the Informed Consent Form (ICF) and who were randomized in the study, regardless of being treated or not.

2.3. Definition of Subgroups

Not applicable

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

Not applicable

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Not applicable

4. PARTICIPANT INFORMATION

4.1. Demographics

Table 3 presents the list of demographic variables that will be reported in the patient profiles.

Table 3: Demographic Variables

Variables
Age (years)
Weight at baseline (kg)
Height at baseline (cm)
Gender (male, female)
Age Group: for adolescent cohort: ≥13 - <18 years for adult cohort: ≥18 - <65 years, ≥ 65 years
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported, Unknown)
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
Country

4.2. Baseline and RSV Disease Characteristics

Table 4 presents the list of baseline and RSV disease characteristics that will be reported in the patient profiles.

Table 4: Baseline and RSV Disease Characteristics

Variables:
Start date and time of first RSV symptoms/signs
Contact with health care professional (HCP) before presenting (no, yes) If yes, type of HCP (General Practitioner, Oncologist, Pneumonologist, Other -specify)
History of wheezing associated with acute respiratory infection (no, yes)
Additional risk factor for severe RSV disease (no, yes) If yes, type • Asthma

Table 4: Baseline and RSV Disease Characteristics

• Chronic Obstructive Pulmonary Disease (COPD) • Congestive Heart Failure (CHF) • Coronary Artery Disease (CAD) • Diabetes Mellitus • Chronic Kidney Disease (CKD) • Other - specify
History of drug allergy (no, yes)
Family history in the allergic/immunologic body system (no, yes, unknown)
History of Tobacco use (current, former, never) (no, yes)
Presence of other respiratory viruses (no, yes) If yes, type of virus Note: based on respiratory pathogens panel assay performed centrally at baseline (influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, bocavirus, or coronavirus)
Presence of respiratory bacteria (no, yes) If yes, type of bacteria Note: based on respiratory pathogens panel assay performed centrally at baseline (streptococcus pneumoniae, staphylococcus aureaus, haemophilus influenzae, moraxella catarrhalis, legionella, mycoplasma pneumoniae, chlamydophila pneumoniae, bordetella pertussis, or bordetella parapertussis)
Presence of SARS-CoV-2 (no, yes) Note: based on respiratory pathogens panel assay performed centrally at baseline

Other baseline characteristics: ie, RSV viral load and subtype, oxygen saturation, RiiQ Symptom Score, respiratory rate and pulse rate will be displayed with actual values over time (see Section 5.2 and Section 6.3).

4.3. HSCT-related characteristics

Table 5 presents the list of HSCT-related characteristics that will be reported in the patient profiles.

Table 5: HSCT-related Characteristics

Variables:
Date of receipt of HSCT
Immunoglobulin level (g/L)
ALC at Screening – central lab test (cells/µL)
ALC category at Screening – local lab test (<200 cells/µL, 200 - <500 cells/µL, ≥500 - <1,000 cells/µL)
ALC category at Screening – central lab test (<200 cells/µL, 200 - <500 cells/µL, ≥500 - <1,000 cells/µL)
Donor type • Autologous • Allogenic matched, related • Allogenic mismatched, related • Allogenic matched, unrelated • Allogenic mismatched, unrelated
Cell source • Bone marrow • Cord blood • Other - specify

Table 5: HSCT-related Characteristics

Underlying disease • Leukemia • Non-Hodgkin lymphoma • Hodgkin disease • Multiple myeloma • Aplastic anemia • Other
If leukemia • Acute lymphocytic • Acute myelogenous • Chronic myelogenous • Other - specify
Underlying disease state at RSV diagnosis • Remission • Minimal Residual Disease • Persistent or Relapse • Unclear
T cell depletion (yes, no)
B cell depletion (yes, no)
Conditioning regimen • Myeloablative • Reduced intensity

4.4. Disposition Information

Table 6 presents a list of the disposition information variables that will be reported in the patient profiles.

Table 6: Disposition information

Variables
Date of signature on informed consent
Eligibility criteria met (no, yes) If no, criterion
Date and time of randomization
Stratification factors at randomization: • Hospitalization status (no, yes) • Lymphophenia at Screening: - <200 cells/µl - 200 to < 500 cells/µl - ≥500 to < 1000 cells/µl • Ribavirin and/or IVIG use (no, yes) If yes, type - Ribavirin use at Randomization (no, yes) - IVIG use at Randomization (no, yes)
Cohort: (Adolescent/Adult)

Table 6: Disposition information

Assigned dosing regimen • 250 mg JNJ-53718678 or matching Placebo twice daily for 21 days • 125 mg JNJ-53718678 or matching Placebo twice daily for 21 days • 125 mg JNJ-53718678 or matching Placebo once daily for 21 days
Treatment group: (Placebo/JNJ-53718678)
Completed the study treatment [Completed (date), Discontinued (date)] If no, reason for treatment discontinuation If withdrawal by subject - Lost to follow-up - Withdrawal of consent or ascent - Death - Other - specify
Completed the study [Completed (date), Discontinued (date)] If no, reason for study discontinuation If withdrawal by subject - Lost to follow-up - Withdrawal of consent or ascent - Death - Other - specify

4.5. Treatment Compliance

Table 7: Treatment compliance

Variables
Date and time of first dose administered
Date and time of last dose administered
Any change in dosing regimen (no, yes) If yes, study Day and new dosing regimen
Any missed doses (no, yes)

4.6. Extent of Exposure

Not applicable

4.7. Protocol Deviations

Protocol deviations will not be reported in the patient profiles.

4.8. Prior and Concomitant Medications

Medications taken from the date when the main study ICF is signed through the end of study will be reported.

In the patient profiles concomitant therapy will be displayed by indication:

- Adverse Even (AE number and term)
- Medical History (Medical history number and term)
- Prophylaxis

- Therapeutic or Diagnostic Procedure (Procedure number and term)
- Trial Indication
- Other

Table 8 presents the list of the concomitant medications variables that will be reported in the patient profiles.

Table 8: Concomitant medications

Variables
Medication or Therapy preferred term using the World Health Organization-Drug Dictionary (WHO-DD)
Start date (study day) AND end date (study day) OR ongoing
Dose with unit; route AND frequency

4.9. Specific Prior Therapy

Corticosteroids related to HSCT, palivizumab, ribavirin, and IV immunoglobulin will be reported in the patient profiles as other prior medication/therapy. It will include the specific therapy taken 30 days prior screening and not ongoing at screening. Ongoing at screening therapy will be reported as concomitant medication.

4.10. Presence of other respiratory viruses or bacteria

Presence of data on other respiratory viruses (other than RSV) or bacteria (both by multiplex PCR) determined in mid-turbinate nasal swabs collected at baseline will be listed (see Table 4).

4.11. Medical History and Family History

Table 9 presents the list of the medical history variables that will be reported in the patient profiles. The family history will not be reported.

Table 9: Medical History

Variables
Has/had the subject any medical history on pre-defined conditions (no, yes) If yes, list the medical history term

5. EFFICACY

Given the small number of patients enrolled, no efficacy analyses will be performed, and no hypothesis will be tested. The efficacy variables presented in the patient profiles are listed below.

5.1. Analysis Specifications

5.1.1. Level of Significance

Not applicable

5.1.2. Data Handling Rules

Not applicable

5.2. Efficacy Endpoint(s)

Table 10 presents the list of efficacy variables that will be reported in the patient profiles.

Table 10: Efficacy

Variables
Plot over time: days since first drug intake – all collected values will be displayed
RiiQ symptom score over time for (defined in Table 11): • all (13) items • the key (7) items, • the upper respiratory tract disease (URTD) symptoms, • the lower respiratory tract disease (LRTD) symptoms, • the body/systemic symptoms Plot including one line per score
Oxygen saturation (SpO_2) [%] over time Plot including color code for oxygen saturation measured on room air (no, yes), value <95% will be flagged.
Log_{10} RSV RNA viral load actual values (log_{10} copies/mL) as measured with qRT-PCR in nasal swab samples over time. In case of co-infection (RSV A and B), plot will include one line per RSV type and combined RSV A and B). Plot including color code for RSV subtype: ie, RSV A, RSV B and RSV A and B
List
Oxygen supplementation (no, yes): If yes, type of supplemental oxygen administration AND [start date (study day) – end date (study day)]
Hospitalization information: [admission date (study day) – hospital discharge date (study day)]
Graft Versus Host Disease (no, yes): If yes, • [start date (study day) – end date (study day)] • Overall severity • Affected Organs • Grade

Table 11: Clinical Course Parameters

Measurement	**Formula**
Symptoms (RiiQ Symptom Scale)	
RiiQ symptom score	RiiQ Symptom Scale is a 13 items questionnaire (see Appendix 3) which ranges from 'None' (score=0; symptom free) to 'Severe' (score=3; severe symptoms). Arithmetic mean will be calculated if at least 9 out of 13 items are available, otherwise it will be set to missing.
RiiQ Key symptom score	Arithmetic mean of the following 7 Key items (nasal congestion, sore throat, short of breath, wheezing, cough, coughing up phlegm [sputum], fatigue [tiredness]) will be calculated if at least 5 out of 7 items are available, otherwise it will be set to missing.
RiiQ URTD symptoms score	Arithmetic mean of the following items (nasal congestion, sore throat) will be calculated if at least 1 out of 2 items are available, otherwise it will be set to missing.

Table 11: Clinical Course Parameters

RiiQ LRTD symptoms score	Arithmetic mean of the following items (cough, wheezing, short of breath, coughing up phlegm [sputum]) will be calculated if at least 3 out of 4 items are available, otherwise it will be set to missing.
RiiQ body/systemic symptoms score	Arithmetic mean of the following items (headache, feeling feverish, body aches and pains, fatigue, neck pain, interrupted sleep, loss of appetite) will be calculated if at least 4 out of 7 items are available, otherwise it will be set to missing.

6. SAFETY

6.1. Adverse Events

Table 12 presents a list of the safety variables that will be reported in the patient profiles.

Table 12: Adverse Events

Variables
Information to be provided for each adverse event
• Preferred term/System organ class • Related to the current respiratory infection: (no, yes) • Event type: ie, Respiratory complications, non-respiratory infectious complications, other • Is there a suspicion of LRTI • Onset: [start date (study day)] • Outcome: ie, Fatal, Not recovered or Not resolved, Recovered or resolved, Recovered or resolved with sequelae, Recovering or resolving, unknown • End date /ongoing • Duration • Toxicity grade • Seriousness criteria: ie, Death, Life threatening, Prolonged/ required hospitalization, Significant disability, Congenital anomaly or birth defect, Other medically important event • Action taken with study treatment • Concomitant or additional therapy • Relationship to study treatment

6.2. Clinical Laboratory Tests

The laboratory abnormalities will be determined according to the Division of Microbiology and Infectious Diseases (DMID) adult toxicity tables (see Appendix 2). In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used.

Table 13 presents the list of clinical laboratory tests that will be reported in the patient profiles.

Table 13: Clinical Laboratory Tests

Variables
Plot over time: days since first drug intake – all collected values will be displayed
Clinical hematology tests including absolute neutrophil count For clinical chemistry tests especially eGFR, creatinine, liver function tests (AST, ALT, direct/indirect/total bilirubin and ALP), cardiac electrolytes: ie, potassium, magnesium, calcium, chloride, phosphorus): • Actual values with toxicity/abnormality flagged will be plotted over time

6.3. Vital Signs

The vital signs abnormalities will be defined as indicated in Table 14.

Table 14: Clinically Important Abnormalities in Vital Signs

Vital Sign	Abnormality Code	Criteria
Systolic blood pressure	Abnormally low	≤ 90 mmHg
	Grade 1 or mild	> 140 mmHg - < 160 mmHg
	Grade 2 or moderate	≥ 160 mmHg - < 180 mmHg
	Grade 3 or severe	≥ 180 mmHg
Diastolic blood pressure	Abnormally low	≤ 50 mmHg
	Grade 1 or mild	> 90 mmHg - < 100 mmHg
	Grade 2 or moderate	≥ 100 mmHg - < 110 mmHg
	Grade 3 or severe	≥ 110 mmHg
Respiratory rate	Grade 1 or mild	17-20 breaths per minute
	Grade 2 or moderate	21-25 breaths per minute
	Grade 3 or severe	> 25 breaths per minute
	Grade 4 or potentially life threatening	intubation
Temperature	Abnormally high	> 38.0 °C
Pulse/Heart Rate	Abnormally low	≤ 45 bpm
	Abnormally high	≥ 120 bpm

Table 15 presents a list of vital signs that will be reported in the patient profiles.

Table 15: Vital signs

Variables
Plot over time: days since first drug intake – all collected values will be displayed
For vital signs parameters including systolic and diastolic blood pressure, heart/pulse rate, respiratory rate, body temperature: • Actual values with abnormality flagged will be plotted over time

6.4. Physical Examination

Not applicable

6.5. Electrocardiogram

The ECG abnormalities will be defined as indicated in Table 16.

Table 16: ECG Abnormalities

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

Table 17 presents the list of ECG parameters that will be reported in the patient profiles.

Table 17: ECG parameters

Variables
Plot over time: days since first drug intake – all collected values will be displayed
For ECG parameters including PR, QT, QTc intervals, and heart rate • Actual values with abnormality flagged will be plotted over time
List
ECG overall interpretation per visit: ie, Normal, Abnormal, Not evaluable

6.6. Hepatotox

Any safety information collected in case of hepatotox will be reported in patient profile.

6.7. Health Economics

Not applicable

6.8. Long-term safety follow-up

Not applicable.

7. VIROLOGY

RSV viral load and RSV subtype will be reported as described in Section 5.2.

Viral Sequencing

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

Baseline samples from all participants will be sequenced to identify pre-existing genetic variations in the F gene. Post-baseline sequencing will be performed during treatment, on the last evaluable on-treatment sample and/or during follow-up for all participants (if viral load is high enough) to

identify emerging amino acid substitutions in the RSV F gene. Additional post-baseline sequencing can be performed on request of the sponsor virologist.

Genetic variations

Genetic variations are defined as changes (on amino acid or nucleotide level) in the participant's viral sequence compared to a reference sequence. Genetic variations can include substitutions, insertions and deletions. The reference sequences used will be RSV-A Long strain (GenBank Accession number AY911262) for RSV-A samples and RSV-B strain 9320 (GenBank Accession number AY353550) for RSV-B samples. Genetic variations will be reported on amino acid level.

- **Baseline genetic variation**: amino acid difference from the RSV-A or RSV-B reference strain detected at baseline with an NGS read frequency $\geq$ 15%.
- **Emerging genetic variation:** a genetic variation (amino acid substitution, insertion or deletion) that is absent, ie, with a NGS read frequency < 3%, at baseline but detected with a NGS read frequency $\geq$ 15% at a later post-baseline time point.
- **Enriched genetic variation**: a genetic variation (amino acid substitution, insertion or deletion) detected at baseline with a NGS read frequency ≥3% and <15%, and with an increase in NGS read frequency of at least 15% post-baseline.
- **Genetic variation profile**: a specific genetic variation or combination of genetic variations at one or more time points.
- **RSV F-gene amino acid positions of interest**:
  - Long list of 24 RSV F protein positions of interest for the class of RSV fusion inhibitors, based on in vitro selection experiments, clinical observations, and/or in vitro reduced susceptibility to RSV fusion inhibitors, as well as residues involved in binding of JNJ-53718678 to the RSV prefusion F protein: positions 127, 137, 138, 140, 141, 143, 144, 323, 338, 339, 392, 394, 396, 397, 398, 399, 400, 401, 474, 486, 487, 488, 489, and 517.

Analysis Time Points

In addition to the time points corresponding to the visits at which samples for RSV F gene sequencing are collected, the below time points will be considered:

- Baseline (BL): Time point with sequencing data available closest prior to the first dose. This will be the Day 1 pre-treatment sample; however, if RSV F gene sequencing data cannot be obtained from this sample, the screening sample may be used for sequencing.
- Last Evaluable On-Treatment Time Point: Last available post-baseline time point during the study treatment phase with sequencing data available. In case no On-Treatment assessment is available, the first assessment during Follow-Up is selected instead.
- Any post-baseline time point in the study with sequencing data available

Table 18 presents the list of virology parameters that will be reported in the patient profiles.

Table 18: Virology parameters

Variables
List
Indicating genetic variations at the 24 RSV F protein positions with enriched/emerging genetic variation flag

8. SUPPORTING DOCUMENTATION

8.1. Appendix 1 List of Abbreviations

AE	adverse event
ALC	Absolute lymphocyte count
AUC	Area under the curve
BMI	body mass index
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical study report
DMID	Division of Microbiology and Infectious Diseases
EAC	Endpoint Adjudication Committee
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic Patient-Reported Outcome
EQ-5D	EuroQol 5-Dimension
EQ-5D-5L	5-level EuroQol 5-Dimension
GVHD	graft-versus-host disease
HCP	Health care professional
HRQOL	health-related quality of life
HSCT	Hematopoietic Stem Cell Transplant
IA	Interim Analysis
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IVIG	intravenous immunoglobulin
IWRS	interactive web response system
LLOQ	lower limit of quantification
LRTC	Lower Respiratory Tract Complication
LRTD	Lower Respiratory Tract Disease
LRTI	Lower Respiratory Tract Infection
LTFU	Long-term follow-up
MRU	medical resource utilization
NGS	next-generation sequencing
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIH	Patient Global Impression of Health
PGIS	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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SOC	Standard-of-care
SpO_2	Peripheral capillary oxygen saturation
UN	United Nations
URTD	Upper Respiratory Tract Disease
URTI	Upper Respiratory Tract Infection
VL	Viral load
WHO-DD	World Health Organization Drug Dictionary

8.2. Appendix 2 DMID Toxicity Tables

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE – 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 flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

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

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

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

MUSCULOSKELETAL				
	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

8.3. Appendix 3 Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)

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.

9. REFERENCES

Spiessens B, Debois, M. Adjusted significance levels for subgroup analyses in clinical trials. Contemp Clin Trials 2010;31:647-656.