Janssen Research & Development*

Clinical Protocol

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of Orally Administered ALS-008176 Regimens in Adult Subjects Hospitalized with Respiratory Syncytial Virus

Protocol 64041575RSV2003; Phase 2b
AMENDMENT 4

ALS-008176 (JNJ-64041575, lumicitabine)

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

EudraCT NUMBER: 2016-001653-40

Status:	Approved
Date:	20 March 2018
Prepared by:	Janssen Research & Development, a Division of Janssen Pharmaceutica NV
EDMS number:	EDMS-ERI-120465461, 9.0

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

Protocol History 64041575RSV2003		
Document Type and *File Name*	Issued Date	Comments
Initial Clinical Protocol *64041575RSV2003_Protocol*	12 May 2016	-
Protocol Amendment 1 *64041575RSV2003_Protocol_Amend_1*	19 July 2016	For details, please refer to Section Amendment 1
Protocol Amendment 2 *64041575RSV2003_Protocol_Amend_2*	13 January 2017	For details, please refer to Section Amendment 2
Protocol Amendment 3 *64041575RSV2003_Protocol_Amend_3*	5 September 2017	For details, please refer to Section Amendment 3
Protocol Amendment 4 *64041575RSV2003_Protocol_Amend_4*	This document	For details, please refer to Section Amendment 4

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (This document)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is for Part 2 of the study (1) to include additional safety samples for biochemistry, (2) to lift the requirement for triplicate electrocardiograms (ECGs) and reduce the ECG timepoints, (3) to prohibit the use of P-glycoprotein (P-gp) inhibitors and inducers, and (4) to optimize the pharmacokinetic (PK) sampling scheme.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: Based on the observed exposure levels and safety/tolerability data generated in Part 1 of the study, the dose regimen for Part 2 of the study will remain unchanged.

SYNOPSIS
3.1 Overview of Study Design
3.2 Study Design Rationale

Rationale: In Part 2 of the study, additional safety samples for biochemistry will be collected on Day 2, Days 3-6, and Day 10, to better characterize the clinical observations of isolated, asymptomatic elevations of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (without concomitant elevations of the bilirubin levels) observed in Part 1 of the study.

Time and Events Schedule

Rationale: A clinical TQT study (Study 64041575RSV1003) showed that ALS-008176 does not induce QTc prolongation of clinical or regulatory concern. Based on this result, the requirement to record triplicate ECGs is lifted for Part 2 of the study, and single ECGs will be performed instead. The ECG timepoints were also reduced.

Time and Events Schedule
9.7 Safety Evaluations

Rationale: Based on recent nonclinical data, ALS-008176 has been demonstrated to be a substrate of P-gp. Since the effect of P-gp inhibitors and inducers on the PK of ALS-008176 and its metabolites in humans is currently unknown, P-gp inhibitors and inducers will be prohibited for 24 hours prior to randomization (14 days for inducers) until 24 hours after the last dose of ALS-008176.

1.1 Background
8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: The PK sampling scheme for Part 2 has been optimized, based on the data of Part 1.

SYNOPSIS
Time and Events Schedule
3.1 Overview of Study Design
9.3.3 Pharmacokinetic Parameters
Attachment 8: Details for Pharmacokinetic Sampling and Collection of Food Intake Information

Rationale: The protocol is aligned with the lumicitabine Investigator's Brochure Ed9.

1 INTRODUCTION
9.9 Benefit-risk Evaluations

Rationale: Minor editorial changes (including alignment with the sponsor's latest available protocol template version), clarifications, and corrections are made, including, but not limited to:
- Clarifying Part 0 of the study.
- Clarify that once all data for Part 1 are collected and the database locked, the sponsor may perform an unblinded, secondary analysis on the full dataset of Part 1, to support clinical development.
- Since Part 1 of the study was already completed at the time of the amendment, all references in the Time and Events Schedule to Part 1 of the study are grayed-out for convenience of the investigator.
- Assure consistency of the wording "increase in treatment duration to *up to* 10 days" throughout the document.
- Clarifying that a paper form of the health-related quality of life (HRQoL) questionnaire should be used (as required by the vendor) by the subject's spouse, partner, relative, friend, or the investigator/-site study personnel trained on the electronic Clinical Outcome Assessment (eCOA) device if the subject is unable to complete the assessment on the device.
- Clarifying the collection of nasal swabs and endotracheal samples (if intubated).
- Correct the statement on the legal age of consent in South Korea.

Throughout the protocol

Amendment 3 (5 September 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment was to remove furosemide, ibuprofen, and trimethoprim/sulfametoxazole from the list of prohibited moderate/strong inhibitors of organic anion transporter (OAT) 3.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: A clinical drug-drug interaction study (Study 64041575RSV1002) between probenecid (strong OAT3 inhibitor) and ALS-008176 showed that probenecid increased the maximum concentration and area under the concentration-time curve from the time of drug administration to the time of the last observation ($AUC_{0\text{-last}}$) of ALS-008112 by 1.28-fold and 1.75-fold, respectively. Based on these data, together with pharmacokinetic (PK)/pharmacodynamic (PD) modeling data, furosemide, ibuprofen, and trimethoprim/sulfametoxazole were removed from the list of prohibited moderate/strong inhibitors of OAT3 as the expected increase on ALS-008112 AUC caused by these drugs was less than 26%, a very mild increase deemed acceptable based on expected exposures using popPK modeling and simulation.

1.1 Background
8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: In countries such as Japan and Taiwan, the legal age of consent is 20 years, and in South Korea it is 19 years. Therefore, the inclusion criterion was adapted to clarify that men or women should have the legal age of consent in the jurisdiction in which the study is taking place.

SYNOPSIS
3 STUDY DESIGN AND RATIONALE
4 SUBJECT POPULATION

Rationale: During study conduct, an issue was identified in which the food intake was not documented in compliance with the protocol. Currently only the electronic case report form (eCRF) allows the documentation of the food intake in relation to the study drug administration in PK forms. No information on food intake can be captured in the electronic Clinical Outcome Assessment (eCOA) for discharged subjects for doses 3 to 10 (maintenance dose [MD] 2 to MD9). Due to the minimal impact of food intake on trough levels (PK sample at Day 7), there will be no adjustments made to the eCOA. No food intake information with regard to study drug administration will be collected for discharged subjects. Furthermore, it is clarified that the food intake information should be recorded in hospitalized subjects only and that the time window should be limited to the food ingested within 30 minutes before or after study drug administration.

TIME AND EVENTS SCHEDULE

Rationale: The protocol is aligned with the sponsor's latest available protocol template and minor editorial changes, clarifications, and corrections were made, including, but not limited to: - Addition of the generic name "lumicitabine". - Corrections were made to consistently state in the protocol that the relationship between the PK and PD (antiviral activity, clinical outcomes, and selected safety parameters) will be evaluated after single and repeated oral administration of ALS-008176. - Clarifications on SpO_2 and ECG assessments in the Time and Events Schedule. - Clarification on details of PK sampling and collection of food intake information in Attachment 8. - Language was added to Section 9.1.2 to allow the use of data of subjects that consented for another Janssen respiratory study. - Correction of a typing eror regarding the relatedness to study drug of the pancytopenia event in the rationale table of protocol amendment 2.
Throughout the protocol

Amendment 2 (13 January 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment was to create a new Part 1 of the study protocol to characterize the pharmacokinetics (PK), to confirm the population pharmacokinetic (popPK) model derived from healthy volunteers in hospitalized adults with respiratory syncytial virus (RSV) infection, and to more clearly define the study eligibility criteria to ensure subject safety.

Furthermore, changes requested by health authorities were made, women of childbearing potential were allowed to participate in the study, the age limit for participants was lowered, the endpoints of the study were updated, subjects on extracorporeal membrane oxygenation were excluded, the guidelines concerning corticosteroid use were adjusted, clarifications regarding the use of the electronic Clinical Outcome Assessment (eCOA) device were added, single electrocardiogram (ECG) measurements were changed to triplicate ECGs, and the dose dispensing instructions were deleted. In addition minor editorial changes, clarifications, and corrections were made.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: Given the report of a probably related serious adverse event (SAE) of reversible pancytopenia in an elderly subject found to have ALS-008112 plasma exposures higher than predicted by the popPK model, a new Part 1 of the study protocol was created to characterize the PK, to confirm the popPK model derived from healthy volunteers in hospitalized adults with RSV infection, and to more clearly define the study eligibility criteria to ensure subject safety. To achieve the objective of characterizing the PK and confirming the popPK model, the study population was more restricted to recruit subjects with criteria more aligned with those of the Phase 1 studies and the PK sampling scheme was updated. Pharmacokinetic modeling data suggest that low body weight and renal impairment may be associated with increased ALS-008112 plasma exposure so these criteria were modified. Furthermore, the plasma exposure of ALS-008112 may also be increased by the concomitant administration of medications which are known inhibitors of organic anion transporter 3 (OAT3). Thus, the following changes were made to the study protocol: - The study design was adapted to include a new Part 1 in the study protocol. In Part 1, the PK will be characterized in the low-dose arm of 750 mg loading dose (LD)/250 mg maintenance dose (MD) ALS-008176 in hospitalized adult subjects infected with RSV. Furthermore, the safety and tolerability of this regimen will be investigated before proceeding to Part 2 of the study which will include the high-dose arm of 1,000 mg LD/500 mg MD ALS-008176. In Part 2, the dose-response relationship of the 750 mg LD/250 mg MD and the 1,000 mg LD/500 mg MD ALS-008176 dosing regimens on antiviral activity will be evaluated. Stratification factors for both parts have been clarified. - The PK sampling scheme was updated to better characterize the PK and to confirm the popPK model. - The inclusion criteria were adjusted to only allow subjects with a body weight of at least 50 kg to participate in the study. - The exclusion criteria were adjusted to disallow subjects who are moderate/severe renally impaired.

- Subjects with hematology laboratory abnormalities at screening, as defined in the protocol, will be excluded.
- List of OAT3 inhibitors which are not allowed during the study and for 24 hours prior to randomization has been updated.

Additional stopping rules were provided to ensure that study drug will be discontinued when the subject has an estimated glomerular filtration rate ≤30 mL/min/1.73 m² according to the Chronic Kidney Disease Epidemiology Collaboration equation and when the subject experiences any of the protocol defined laboratory abnormalities.

SYNOPSIS
TIME AND EVENTS SCHEDULE
1 INTRODUCTION
2 OBJECTIVES, ENDPOINTS, AND HYPOTHESIS
3 STUDY DESIGN AND RATIONALE
4.1 Inclusion Criteria
4.2 Exclusion Criteria
5 TREATMENT ALLOCATION AND BLINDING
6 DOSAGE AND ADMINISTRATION
9.7.1 Specific Toxicities
8 PRESTUDY AND CONCOMITANT THERAPY
9.3 Pharmacokinetics
9.9 Benefit-risk Evaluations
10.2 Discontinuation of Study Treatment/Withdrawal From the Study
11 STATISTICAL METHODS

Rationale: The following changes were made upon health authority request:

- Addition of a mandatory safety sample for hematology and biochemistry on the Day 28 follow-up visit, to ensure a comprehensive safety evaluation in all subjects.
- Addition of a follow-up visit 2 days after the last treatment dose for subjects who discontinued treatment early, to be consistent with the Day 7 follow-up visit planned for subjects who completed treatment.
- Adjustment of the inclusion criteria, exclusion criteria, and potential risk sections to be consistent with recommendations related to contraception and pregnancy testing in clinical trials as described in the Clinical Trial Facilitation Group (CTFG) guidance.[8]
    - Extension of the duration of contraception (ie, from 90 to 104 days for men and their female partners of childbearing potential, and from 30 to 44 days for heterosexually active women of childbearing potential).
    - Adjustment of the duration in which female participants are not allowed to donate eggs (ova, oocytes).
    - Clarification of the contraceptive methods recommended for female partners (if of childbearing potential) of male participants.
- Given that prescription medications such as palivizumab, ribavirin, and intravenous immunoglobulin used to prevent or treat RSV infection have a half-life that goes beyond 3 days, they have been included in the list of disallowed concomitant medications as prohibited 30 days or 5 half-lives (whichever is longer) before the planned first dose of study drug. Furthermore, it was clarified that prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.
- Adjustment of the definition of the intent-to-treat (ITT) infected population.
- Clarification that the key findings of the popPK and PK/pharmacodynamic (PD) analysis of this study will be presented in the final clinical study report.
- Clarification that the interim analysis will be performed upon treatment completion (rather than randomization) by 45 subjects to ensure that adequate data is available for interim analysis review.

SYNOPSIS
TIME AND EVENTS SCHEDULE
4.1 Inclusion Criteria
4.2 Exclusion Criteria
8 PRESTUDY AND CONCOMITANT THERAPY
9.1.4 Posttreatment Phase (Follow-up)
9.9.4 Potential Risks
11 STATISTICAL METHODS
11.4 Pharmacokinetic Analyses
11.6 Pharmacokinetic/Pharmacodynamic Analyses
11.11 Interim Analysis

REFERENCES
Rationale: Based on recent nonclinical toxicology data from embryo-fetal development studies in rats and rabbits, and fertility and early embryonic development to implantation studies in rats, the inclusion criteria were adjusted to allow women of childbearing potential to participate in the study. Furthermore, serum pregnancy testing was replaced by urine pregnancy testing and the definition of women not of childbearing potential was clarified. Contraceptive requirements for heterosexually active women of childbearing potential were added and details regarding the risk for potential PK drug-drug interaction between ALS-008176 and hormonal contraceptives were provided.
TIME AND EVENTS SCHEDULE 1.1 Background 4.1 Inclusion Criteria 9.7 Safety Evaluations 9.9.4 Potential Risks
Rationale: With the availability of the results from embryo-fetal development studies in rats and rabbits, and fertility and early embryonic development to implantation studies in rats, the age limit for participants was lowered to 18 years. The stratification by age was also adjusted to be in line with the lowered age limit for participation in the study.
SYNOPSIS 3 STUDY DESIGN AND RATIONALE 4 SUBJECT POPULATION 5 TREATMENT ALLOCATION AND BLINDING
Rationale: The following changes were made to the endpoints: - The determination of the RSV RNA viral load area under the curve (AUC) in subjects assigned to a longer dosing duration, if dosing duration is increased by the Independent Data Monitoring Committee (IDMC), was moved from the primary to the secondary endpoints. - For clarity, the secondary endpoint "Number of hours until peripheral capillary oxygen saturation (SpO_2) ≥93% on room air among subjects who were not on supplemental oxygen prior to current hospitalization" was changed to "Number of hours until peripheral capillary oxygen saturation (SpO_2) ≥93% on room air among subjects who were not on supplemental oxygen prior to the onset of respiratory symptoms". - The exploratory endpoint of disease status and presence of complications with onset after treatment initiation was adjusted to include respiratory failure and other RSV-related complications to harmonize with the electronic case report form (eCRF). - Added that if the dosing duration is increased by the IDMC to up to 10 days, supplemental oxygen above pre-RSV disease level will be measured from treatment initiation until 1 day after the last dose of study drug.
SYNOPSIS 2.1.2 Endpoints
Rationale: It was clarified that RSV RNA viral load (AUC) will be measured in mid-turbinate nasal swabs of non-intubated subjects or in both mid-turbinate nasal swabs and endotracheal samples of intubated subjects. Furthermore, it was clarified that mid-turbinate nasal swabs (if non-intubated) or endotracheal samples (if intubated) will be collected during screening to confirm RSV infection and to assess for viral and bacterial co-infection.
SYNOPSIS TIME AND EVENTS SCHEDULE 2.1.1 Objectives 2.1.2 Endpoints 9.1.2 Screening Phase 9.1.3 Double-blind Treatment Phase 9.2 Efficacy Evaluations 9.8 Other Evaluations

Rationale: Subjects who are being treated with extracorporeal membrane oxygenation are excluded from participation in the study.
4.2 Exclusion Criteria
Rationale: The use of systemic corticosteroids before and during the study was clarified to avoid misunderstanding since it is anticipated that a significant proportion of the subjects is expected to suffer from chronic obstructive pulmonary disease (COPD) or asthma, wherefore treatment with corticosteriods is considered standard of care.
4.2 Exclusion Criteria 8 PRESTUDY AND CONCOMITANT THERAPY
Rationale: The guidelines regarding the use of the eCOA device were adjusted: - Clarification of the situations in which trained investigator/study-site personnel can complete the eCOA on the subject's behalf. - Use of the electronic case report form (eCRF) instead of the eCOA device for the Katz Activities of Daily Living (ADL) assessment as this is an assessment to be completed by the investigator.
TIME AND EVENTS SCHEDULE 9.1.1 Overview 11.7 Subject Clinical Outcome Assessments 11.8 Katz Activities of Daily Living 17.4 Source Documentation 17.5.1 Katz Activities of Daily Living 17.6 Subject Clinical Outcome Assessments
Rationale: Change from single to triplicate ECG measurements at screening, on Day 1, and on Day 7 to improve the precision of the measurements. Additionally triplicate ECGs were added on Day 28.
TIME AND EVENTS SCHEDULE 9.7 Safety Evaluations
Rationale: Deletion of the dose dispensing instructions from the list of study-specific materials. These instructions are part of the study-site investigational product and procedures manual and the subject eCOA device.
15 STUDY-SPECIFIC MATERIALS
Rationale: Minor editorial changes, clarifications, and corrections were made.
Throughout the protocol

Amendment 1 (19 July 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to add an inclusion criteria for female subjects regarding the donation of eggs and to add a section on rash management. Additionally, the protocol is aligned with the sponsor's latest available protocol template and minor editorial changes, clarifications, and corrections are made.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: An inclusion criteria was added to assure that woman agree not to donate eggs (ova, oocytes) during the study and for at least 90 days after receiving the last dose of study drug.
4.1 Inclusion Criteria 9.9.4 Potential Risks

Rationale: Rash management was added in the section of "Specific Toxicities" to align with the Phase 2b pediatric study protocol. A visit schedule for rash management for adult subjects was added in Attachment 7.

9.7 Safety Evaluations
Attachment 7

Rationale: The following changes were made to align with the sponsor's latest available protocol template:
- Added a leading phrase to inclusion criteria 9 and 10 indicating that contraceptive use by men or women should be consistent with local regulations.
- Revised prohibitions and restrictions criterion 2 to indicate that "all requirements must be met during the study as noted in the Inclusion and Exclusion Criteria".

4.1 Inclusion Criteria
4.3 Prohibitions and Restrictions

Rationale: Minor editorial changes, clarifications, and corrections were made, including, but not limited to:
- Correction of the loading dose of regimen C to 1,000 mg.
- Correction of the timing of study drug administration to no later than 4h after randomization.
- Clarification in the protocol that the spirometry and diffusing capacity of the lung for carbon monoxide (DLCO) tests will only be performed if available at the study site and the clinical condition of the subject allows testing as judged by the investigator.
- Addition of extra blood samples for exploratory biomarker analysis (host RNA).
- Inclusion of the most recent version of the Respiratory Infection Symptom Questionnaire© in Attachment 2.

Throughout the protocol
SYNOPSIS
TIME AND EVENTS SCHEDULE
3 STUDY DESIGN AND RATIONALE
9.1 Study Procedures
9.5 Biomarkers
9.8 Other Evaluations
15 STUDY-SPECIFIC MATERIALS
Attachment 2

SYNOPSIS

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of Orally Administered ALS-008176 Regimens in Adult Subjects Hospitalized with Respiratory Syncytial Virus

ALS-008176 (also known as JNJ-64041575 or lumicitabine) is a 3',5'-bisisobutyrate prodrug, which is readily metabolized to the cytidine nucleoside analog polymerase inhibitor ALS-008112. Subsequently, inside cells, ALS-008112 is efficiently converted to its nucleoside triphosphate (NTP), ALS-008136. This NTP is a selective inhibitor of respiratory syncytial virus (RSV) ribonucleic acid (RNA)-dependent RNA polymerase activity and works via a classic chain termination mechanism. ALS-008144, the uridine analog metabolite of ALS-008112, is the inactive major metabolite noted in systemic circulation.

Investigational Product and its Metabolites

Compound Number	Description
ALS-008176 (JNJ-64041575, lumicitabine)	3',5'-bisisobutyrate prodrug of ALS-008112
ALS-008112 (JNJ-63549109)	parent nucleoside analog, major metabolite of ALS-008176, inactive
ALS-008206 (JNJ-64412309)	3'-isobutyrate monoester of ALS-008112, minor metabolite, inactive
ALS-008207 (JNJ-64412296)	5'-isobutyrate monoester of ALS-008112, minor metabolite, inactive
ALS-008144 (JNJ-64167896)	uridine analog metabolite of ALS-008112, major metabolite, inactive
ALS-008136 (JNJ-65409136)	5'-triphosphate of ALS-008112 (NTP), intracellular metabolite, active
ALS-008137 (JNJ-65409123)	5'-monophosphate of ALS-008112, intracellular metabolite, inactive

Abbreviation: NTP: nucleoside triphosphate.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

For Part 1:

The primary objective is to characterize the pharmacokinetics (PK) and to confirm the population PK (popPK) model derived from healthy volunteers in hospitalized adults who are infected with RSV.

For Part 2:

The primary objective is to determine in hospitalized adults who are infected with RSV the dose-response relationship of multiple regimens of ALS-008176 on antiviral activity based on nasal RSV shedding using quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) assay.

Secondary Objectives

The secondary objectives for Part 1 and Part 2 are to determine in hospitalized adults who are infected with RSV:

- The safety and tolerability of ALS-008176.
- The impact of ALS-008176 on the clinical course of RSV infection including:
  - Duration of hospital stay.
  - Duration of supplemental oxygen.
  - Evolution of Activities of Daily Living (ADL) as assessed by Katz ADL score.
  - Time to clinical stability.

  - Improvement on the ordinal scale.
  - Rate of mortality and complications.
- The antiviral activity based on nasal RSV shedding using qRT-PCR assay (secondary for Part 1 only) and the time to cessation of nasal RSV shedding.
- The impact of ALS-008176 on the emergence of resistant strains of RSV.
- The PK of ALS-008112 and ALS-008144 (and other metabolites, if applicable) in plasma.
- The relationship between the PK and pharmacodynamics (PD; antiviral activity, clinical symptoms, and selected safety parameters) after single (loading dose [LD]) and repeated oral dosing (maintenance dose [MD]) of ALS-008176.

Exploratory Objectives

The exploratory objectives for Part 1 and Part 2 are to evaluate in hospitalized adults who are infected with RSV:

- The relationship between viral kinetics and clinical outcome, including the relationship between RSV RNA viral load and:
  - Oxygen supplementation.
  - Duration of hospitalization.
  - Katz ADL score.
  - Clinical stability.
- The impact of the baseline viral subtype and genotype on the antiviral activity.
- Onset of complications after initiation of treatment.
- The impact of ALS-008176 on the clinical course of RSV during and following hospitalization as assessed by the subject in the electronic Clinical Outcome Assessment (eCOA) using various scoring systems.
- The impact of RSV and its treatment on health-related quality of life (HRQoL) as assessed by the subject in the eCOA.
- The relationship between the Katz ADL score and the subject eCOA responses.
- Medical resource utilization to manage subjects.
- The comparison of the RSV RNA viral loads measured in mid-turbinate nasal swabs and endotracheal samples from intubated subjects.
- To explore the evolution of diffusing capacity of the lung for carbon monoxide (DLCO) and spirometry in subjects hospitalized with RSV infection.

Additionally, the impact of ALS-008176 on the infectious viral load may be evaluated using a quantitative culture of RSV (plaque assay) on a selected number of subjects and samples (mid-turbinate nasal swabs [if non-intubated] or mid-turbinate nasal swabs and endotracheal samples [if intubated]) at the sponsor's discretion.

Endpoints

Primary Endpoints

For Part 1:

The primary endpoint is the PK of ALS-008112 and ALS-008144 (and other metabolites, if applicable) in plasma.

For Part 2:

The primary endpoint is RSV RNA viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) area under the curve (AUC) from immediately prior to first dose of study drug (baseline) until Day 7.

Secondary Endpoints

The secondary endpoints for Part 1 and Part 2 are:

- Safety/tolerability including adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.
- RSV clinical course endpoints:
  - Length of hospital stay from admission to discharge and from study treatment initiation to discharge.
  - Length of hospital stay from admission to readiness for discharge and from study treatment initiation to readiness for discharge, with readiness for discharge defined by the investigator.
  - Need for and duration of intensive care unit (ICU) stay.
  - Need for and duration of supplemental oxygen (regardless of method used).
  - Number of hours until peripheral capillary oxygen saturation (SpO_2) ≥93% on room air among subjects who were not on supplemental oxygen prior to the onset of respiratory symptoms.
  - Respiratory rate, SpO_2, and body temperature return to pre-RSV disease level.
  - Need for and duration of noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).
  - Time to return to pre-RSV functional status (Katz ADL score).
  - Need for hydration and feeding by intravenous (IV) catheter/nasogastric tube.
  - Time to clinical stability defined as the time at which the following criteria are all met:
    - normalization of blood oxygen level (return to baseline; by pulse oximetry) without requirement of supplemental oxygen beyond baseline level
    - normalization of oral feeding
    - normalization of respiratory rate
    - normalization of heart rate
  - Improvement on the ordinal scale.
  - All-cause mortality.

- RSV RNA viral load as measured by qRT-PCR of the mid-turbinate nasal swab specimens which will be used to determine the following:
  - Viral load over time.
  - Peak viral load, time to peak viral load, rate of decline of viral load, and time to RSV RNA being undetectable.
  - Proportion of subjects with undetectable viral load at each time point.
  - The RSV RNA viral load AUC from immediately prior to first dose of study drug (baseline) until Day 7 (secondary for Part 1 only).
  - RSV RNA viral load AUC from immediately prior to first dose of study drug (baseline) until Day 10 and until Day 14.
  - RSV RNA viral load AUC in subjects assigned to a longer dosing duration, if dosing duration is increased by the Independent Data Monitoring Committee (IDMC), from baseline until 1 day after the last dose of study drug (Part 2 only).
- Sequence changes (postbaseline) in the RSV polymerase L-gene and other regions (only if no mutations are seen in the L-gene) of the RSV genome compared with baseline sequences.
- Population-derived PK parameters of ALS-008112.

Exploratory Endpoints

The exploratory endpoints for Part 1 and Part 2 are:

- The amount of:
  - Supplemental oxygen above pre-RSV disease level (regardless of method used) from study treatment initiation to Day 7.

    NOTE: If the dosing duration is increased by the IDMC to up to 10 days, supplemental oxygen above pre-RSV disease level will be measured from treatment initiation until 1 day after the last dose of study drug.
  - Oxygen delivered by noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).
  - Subjects (proportion) who started antibiotic use after the first dose of the study drug.
- Disease status and presence of complications with onset after treatment initiation:
  - Bacterial superinfections reported as AEs (eg, pneumonia, acute otitis media, sinusitis, bronchitis, bacteremia).
  - Exacerbations of underlying pulmonary disease (eg, asthma, chronic obstructive pulmonary disease).
  - Cardiovascular and cerebrovascular events (eg, myocardial infarction, congestive heart failure exacerbation, arrhythmia, stroke).
  - Respiratory failure.
  - *Clostridium difficile* associated diarrhea.
  - Other RSV-related complications.

- Duration and severity of signs and symptoms of RSV infection as assessed by the respiratory infection patient-reported outcome (RI-PRO) questionnaire and additional questions about health and functioning completed by the subject in the eCOA.
- HRQoL assessed by the EuroQoL 5 Dimension 5 level version (EQ-5D-5L) completed by the subject in the eCOA.
- Hospital readmission for respiratory reasons up to the Day 28 follow-up visit.
- Medical resource utilization.
- RSV RNA viral load (AUC) as measured by qRT-PCR of mid-turbinate nasal swabs and endotracheal samples in intubated subjects.
- Lung function measured by the DLCO and spirometry test.
- RSV infectious viral load as measured using a quantitative viral culture (plaque assay).

Hypothesis

For Part 1, no formal hypothesis is specified. Part 1 is intended to characterize the PK in the low-dose arm of 750 mg LD/250 mg MD ALS-008176 and to confirm the popPK model derived from healthy volunteers in hospitalized adult subjects infected with RSV. Furthermore, the safety and tolerability of this regimen will be investigated before proceeding to Part 2 of the study which will include the high-dose arm of 1,000 mg LD/500 mg MD ALS-008176.

For Part 2, the primary hypothesis is that there is a positive dose-response relationship of active treatment on the average RSV RNA viral load AUC with the average AUC on at least 1 of the active treatments being lower than the average AUC on placebo.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-finding study of ALS-008176 in hospitalized adults of ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) who are infected with RSV. The study will be performed in 2 parts.

Part 1

A target of approximately 24 subjects with a maximum of 36 subjects will be randomized in a 1:2 ratio to Regimen A or B:

- Regimen A (placebo): a single LD (Dose 1) followed by 9 MDs (Doses 2 to 10) of matching placebo, administered twice daily.
- Regimen B (low-dose ALS-008176): a single 750 mg LD (Dose 1) followed by nine 250 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.

The IDMC will review the safety and PK data after approximately 12 subjects have completed treatment as per the IDMC charter. When approximately 24 subjects have completed the Day 14 follow-up visit, an unblinded primary analysis will be performed by the sponsor, for review by the IDMC. Further enrollment in this part of the study up to 36 subjects may continue while the data are being analyzed. Once all data for Part 1 are collected and the database locked, the sponsor may perform an unblinded, secondary analysis on the full dataset of Part 1, to support clinical development.

Part 2

A target of approximately 90 subjects will be randomized in a 1:1:1 ratio to Regimen A, B, or C with approximately 30 subjects planned per treatment regimen:

- Regimen A (placebo): a single LD (Dose 1) followed by 9 MDs (Doses 2 to 10) of matching placebo, administered twice daily.
- Regimen B (low-dose ALS-008176): a single 750 mg LD (Dose 1) followed by nine 250 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.
- Regimen C (high-dose ALS-008176): a single 1,000 mg LD (Dose 1) followed by nine 500 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.

Each part of the study will be conducted in 3 phases: a screening phase, a treatment phase from Day 1 to Day 5/6 (depending on the timing of the LD administration), and a follow-up phase for a total of 28 days post randomization. Subjects will have assessments completed during hospitalization and at the Day 7, Day 10, Day 14, and Day 28 visits. Depending on discharge date, assessments will be completed either while hospitalized or during outpatient visits. For hospitalized subjects additional assessments are done as per the Time and Events Schedule. The duration of the subject's participation will be approximately 28 days, screening period not included.

Pharmacokinetic assessments will be performed using a popPK model. Intensive PK sampling in Part 1 of this study will be used to update and confirm the popPK model that was developed based on the data from healthy volunteers. Based on the PK data from hospitalized adult subjects infected with RSV from Part 1 of this study, the PK sampling for Part 2 was optimized. The popPK model may be further modified or adapted as needed.

An unblinded IDMC will be commissioned for this study and a Sponsor Committee will be established. For Part 1, the IDMC will review the safety and PK data as described above. In Part 2, based on the reviews of PK, efficacy, and safety data, changes to enrollment in the treatment arms, dose regimen adjustments, or an increase in dose duration to up to 10 days may be implemented. In Part 2, a maximum of 2 formal interim analyses are planned to assess the primary endpoint for early superiority and futility. The first formal interim analysis will be performed when at least 45 subjects have completed treatment to ensure that adequate data is available for interim analysis review, preferably after the end of a hemispheric RSV season. If the study is considered underpowered, a sample size increase may be suggested to a maximum of 180 subjects.

SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible following admission to the emergency room or hospitalization, such that subjects are randomized within 5 days of RSV symptom onset. Men or women ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) diagnosed with RSV infection based on a polymerase chain reaction (PCR)-based diagnostic assay (with or without co-infection with another respiratory pathogen) who have been (or will be) admitted to the hospital and who have signed informed consent will be enrolled. Subjects who were admitted to the hospital for another cause but develop an acute respiratory illness while being hospitalized are also eligible for screening.

DOSAGE AND ADMINISTRATION

The study drug ALS-008176 will be provided as tablets for oral administration. Study drug administration should start as soon as possible, but no later than 4 hours after randomization in order to maximize the opportunity for the compound to inhibit viral replication and potentially improve outcomes.

Subjects will be dosed with a single LD followed by 9 MDs twice daily (at least 8 hours apart and maximum 16 hours apart, with no more than 2 doses per calendar day) during Day 1 to Day 5/6

(depending on the timing of the LD administration). In Part 1, subjects will be randomized in a 1:2 ratio to Regimen A or B. In Part 2, subjects will be randomized in a 1:1:1 ratio to Regimen A, B, or C.

	Regimen A[a]	**Regimen B**[a]	**Regimen C**[a]
Treatment Regimen	Placebo	Low-dose ALS-008176: 750 mg LD/250 mg MD	High-dose ALS-008176: 1000 mg LD/500 mg MD
Loading Dose	Placebo: 1 intake of 3 tablets	ALS-008176: 1 intake of 3 x 250 mg tablet	ALS-008176: 1 intake of 2 x 500 mg tablet Placebo: 1 intake of 1 tablet
Maintenance Dose	Placebo: 9 intakes of 1 tablet	ALS-008176: 9 intakes of 1 x 250 mg tablet	ALS-008176: 9 intakes of 1 x 500 mg tablet

[a] Placebo tablets will be visually identical to their active drug counterparts

Administration of each dose should occur at approximately the same time each day. ALS-008176 can be administered without regard to food.

EFFICACY EVALUATIONS

Table 1 describes the efficacy evaluations to be performed.

Table 1: Summary of Efficacy Evaluations

Evaluation	Purpose
Viral Load Determination	Evaluation of antiviral activity of ALS-008176; RSV RNA viral load will be measured in mid-turbinate nasal swabs (obtained from non-intubated subjects) or in mid-turbinate nasal swabs and endotracheal samples (obtained from intubated subjects or via suction through tracheostomy or other sampling methods) using qRT-PCR performed at the central laboratory. RSV infectious viral load may be measured in mid-turbinate nasal swabs (if non-intubated) or mid-turbinate nasal swabs and endotracheal samples (if intubated) using a quantitative culture method (plaque assay) in a selected number of subjects and samples at the sponsor's discretion.
Viral Resistance	To identify preexisting sequence polymorphisms and to characterize emerging RSV variants: viral resistance will be performed by sequencing the polymerase L-gene and other regions (only if no mutations are seen in the L-gene) of the RSV genome in samples taken before treatment (at baseline), during treatment, and posttreatment.
Clinical Evaluation	• Clinical evaluation including, but not limited to: – Oxygen requirement type (eg, supplemental oxygen, noninvasive positive pressure ventilation, endotracheal-mechanical ventilation, mechanical ventilation by tracheostomy), duration, and amount. – Body weight. – Respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, and body temperature. – SpO_2. – Level of hospital care (eg, ICU, transitional care unit, ward floor). – Duration of hospitalization. – Need for hydration and feeding by IV catheter/nasogastric tube. – Functional status (Katz ADL score).
Subject Evaluation	• Evaluation of RSV disease-related signs and symptoms and additional questions about health and functioning. • HRQoL (EQ-5D-5L).

Abbreviations: ADL: Activities of Daily Living; EQ-5D-5L: EuroQol 5 Dimension 5 level version; HRQoL: health-related quality of life; ICU: intensive care unit; qRT-PCR: quantitative reverse transcriptase-polymerase chain reaction; RSV: respiratory syncytial virus; RNA: ribonucleic acid; SpO_2: peripheral capillary oxygen saturation.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be analyzed to determine concentrations of ALS-008112 and ALS-008144 (and other metabolites, if applicable).

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

The relationship between the PK and PD (antiviral activity, clinical outcomes, and selected safety parameters) after single and repeated oral administration of ALS-008176 will be evaluated.

BIOMARKER EVALUATIONS

Blood samples will be collected for exploratory biomarker analyses (host RNA), on the premise that these markers may play a role in the treatment response, PK, safety of ALS-008176, or the status and change of the RSV-related disease. In addition, leftover mid-turbinate nasal swabs or blood samples collected for other testing may be used for biomarker analysis (eg, proteins including cytokines) if available on the same premise.

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

No human deoxyribonucleic acid analyses will take place on these samples.

MEDICAL RESOURCE USAGE AND HEALTH ECONOMICS

Collected data may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalization (total days length of stay, including duration by wards [eg, ICU]).
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medication).
- Need for, and duration of, nursing home or health services from baseline to Day 28.

SAFETY EVALUATIONS

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

An IDMC will be established to monitor the safety of subjects and will review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in this study and to evaluate whether efficacy objectives are met. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

For Part 1, the IDMC will review the safety and PK data after approximately 12 subjects have completed treatment as per the IDMC charter. When approximately 24 subjects have completed the Day 14 follow-up visit, an unblinded primary analysis will be performed by the sponsor, for review by the IDMC. Further enrollment in this part of the study up to 36 subjects may continue while the data are being analyzed. Once all data for Part 1 are collected and the database locked, the sponsor may perform an unblinded, secondary analysis on the full dataset of Part 1, to support clinical development.

For Part 2, the IDMC will review the safety data, initially after approximately 12 subjects have completed treatment and when approximately 12 Japanese subjects have completed treatment to assess that treatment may safely continue in each arm.

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

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

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and other safety evaluations.

STATISTICAL METHODS

No formal hypothesis is specified for Part 1 of this study. Part 1 is intended to characterize the PK and to confirm the popPK model derived from healthy volunteers in hospitalized adult subjects infected with RSV. Furthermore the safety and tolerability of the low-dose ALS-008176 treatment regimen will be assessed. The number of subjects participating in Part 1 is considered sufficient to achieve the objectives of the characterization of the PK in Part 1 and allows for updating the PK model, if deemed necessary, based on the results (potential covariates) found in Part 1.

A total sample size of 15 to 16 subjects on active treatment would provide 80% power to achieve a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and central volume of distribution, assuming a between subject variation of 50% (coefficient of variation) as based on 10,000 simulations of the current popPK model. For the secondary objective of safety assessment the probability was calculated to observe an (S)AE that has a true incidence of 1% which would be 15% with a total sample size of 16 subjects on active treatment; the probability to observe an (S)AE with a true incidence of 0.1%, 0.5% and 0.8% is 2%, 8% and 12%, respectively. Therefore, the current sample size of 16 subjects on active treatment is deemed adequate for Part 1.

For Part 2, the primary hypothesis of a positive dose-response relationship assumes that dose regimens with higher exposure with respect to MD will have at least an equal or better effect on viral load. Therefore 2 contrasts will be tested at each of the interim analysis points and final analysis; a contrast with no difference between the 2 active regimens tested against placebo and a contrast with a positive linear dose-response relationship with respect to active regimens. With respect to multiple contrast testing, multiplicity will be controlled at the prespecified (interim) alpha level by calculating adjusted p-values from the simulated distribution of the maximum or maximum absolute value of a multivariate t random vector (ie, using the correlation between the contrasts to optimally control for alpha). The overall (family-wise) type 1 error rate of 2.5% (1-sided) will be adjusted for multiple testing due to formal interim analyses using an O'Brien-Fleming alpha spending function with 3 sequential tests (2 interim, 1 final). As based on 10,000 simulations a sample size of 90 subjects randomized in a 1:1:1 ratio (placebo: low-dose ALS-008176: high-dose ALS-008176) will offer approximately 90% power to detect a positive dose-response relationship as defined assuming an effect size of 0.77 using Cohen's d (ie, the effect size expressed as the ratio of the standard deviation of the AUC) and approximately 80% power assuming an effect size of 0.67 (Cohen's d). Based on the results of the ALS-008176 RSV human challenge study, these effect sizes were considered plausible. The results of Part 1 did not lead to changes in the assumptions underlying the sample size determination.

For Part 2, the primary endpoint in this study is RSV RNA $\log_{10}$ viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) AUC immediately prior to first dose of study drug (baseline) over 7 days. Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors over time. The differences in the AUCs for active versus placebo will be derived using appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals. For inferential purposes, p-values will be compared with significance levels controlling for the (family-wise) type 1 error rate.

Population PK analysis of plasma concentration-time data of ALS-008112 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (eg, demographics, laboratory variables, race) will be tested as potential covariates affecting PK parameters.

Statistical approaches to explore correlations between clinical outcome and biomarkers in blood and mid-turbinate nasal swabs vary and depend on the different data types of the applied technology

platforms, as well as on the extent of observed differences among study subjects. Analyses may be conducted at the sponsor's discretion and reported separately from this study.

Efficacy and safety parameters will be subject to PK/PD analysis. ALS-008112 exposures will be evaluated as an independent variable, with selected efficacy and selected safety parameters considered as dependent variables. Various approaches, including graphical analysis, linear, nonlinear, and logistic regression methods may be utilized.

Subject-reported eCOA (RI-PRO, additional questions about health and functioning, and HRQoL [EQ-5D-5L]), investigator-reported Katz ADL data, medical resource utilization, and health economics assessments will be descriptively summarized by treatment group and compared across treatment groups.

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

TIME AND EVENTS SCHEDULE

Phase	Screening	Treatment Phase			Follow-up Phase[a]						
Day	0	1	2	3 to 6[b]	7 (+2 days)[c]	8 to 9[d]	10 (+2 days)	11 to 13[d]	14 (+2 days)	15 to 27	28 (±2 days) EoS[e]
Study Procedure											
Screening/Administrative											
Informed consent	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria[f]	X										
Urine pregnancy test (all female subjects)	X										X
Study Drug Administration		1 LD followed by 9 MDs MDs may be extended up to 19 doses over 10 days if recommended by the IDMC									
Randomization		X									
Dispense study drug[h]		X	X	X							
Study drug log[i]				X							
Clinical Efficacy Evaluations											
Ordinal scale assessment				X[z]							
Subject eCOA[j]	X	X[k]	X	X	X	X	X	X	X	X	X
Clinical evaluation[l]	X	X	X	X	X	X	X	X	X		X
Katz ADL[m]	X	X	X	X	X		X		X		X
Oxygen saturation (SpO_2)[n]	X (Q4h)	X (Q4h)	X (Q4h)	X (Q4h)	X (Q4h)	X (Q8h)	X (Q8h)	X (Q8h)	X		X
Medical resource utilization and health economics assessment	X				X				X		X
DLCO and spirometry[o]		X			X						X
Clinical Safety Evaluations											
Physical examination[p]	X	X	X		X	X[g]	X	X[g]	X		X
Vital signs[q]	X	bid	bid	bid	X	X[g]	X	X[g]	X		X
Part 1: Triplicate 12-lead ECG[r]	X	X			X				X[r]		X
Part 2: Single 12-lead ECG[r]	X			X							X

Phase	Screening	Treatment Phase			Follow-up Phase[a]						
Day	0	1	2	3 to 6[b]	7 (+2 days)[c]	8 to 9[d]	10 (+2 days)	11 to 13[d]	14 (+2 days)	15 to 27	28 (±2 days) EoS[e]
Study Procedure											
Nasal Swabs											
Mid-turbinate nasal swab (if non-intubated) or endotracheal sample (if intubated): RSV diagnosis confirmation, viral and bacterial co-infection[s]	X										
Mid-turbinate nasal swab (if non-intubated) or mid-turbinate nasal swab and endotracheal sample (if intubated): RSV RNA viral load, viral resistance (genome sequencing), biomarker and infectious virus (plaque assays)[s, t]		X[u]	X	X	X		X		X		X
Clinical Laboratory Assessments (Performed in Local Laboratory)											
Blood sampling for hematology[v]	X		X	X	X		X		X		X
Part 1: Blood sampling for biochemistry[v]	X				X				X		X
Part 2: Blood sampling for biochemistry[v]	X		X	X	X		X		X		X
Urinalysis[v]		X			X				X		
Pharmacokinetics											
Blood sampling for pharmacokinetics[w]		X	X	X	X		X				
Biomarkers											
Blood sampling for biomarkers (host RNA)	X	X	X		X				X		
Ongoing Subject Review											
Concomitant therapy[x]	X	X	X	X	X	X	X	X	X	X	X
Adverse events[y]	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADL: Activities of Daily Living; AE: adverse event; bid: twice daily; CPE: complete physical examination; DBP: diastolic blood pressure; DLCO: diffusing capacity of the lung for carbon monoxide; DPE: directed physical examination; ECG: electrocardiogram; eCOA: electronic Clinical Outcome Assessment; eCRF: electronic case report form; EoS: end of study; EQ-5D-5L: EuroQol 5 Dimension 5 level version; HRQoL: health-related quality of life; ICF: informed consent form; IDMC: Independent Data Monitoring Committee; LD: loading dose; MD: maintenance dose; PK: pharmacokinetic(s); Q4h: every 4 hours; Q8h: every 8 hours; RI-PRO: respiratory infection patient-reported outcome; RNA: ribonucleic acid; RSV: respiratory syncytial virus; SAE: serious adverse event; SBP: systolic blood pressure; SpO_2: peripheral capillary oxygen saturation.

Footnotes:

a. If a subject is discontinued from study drug, a follow-up visit will be scheduled 2 days (+2 days), 5 days (+2 days), 9 days (+2 days), and 23 days (±2 days) after the last dose of study drug was administered. Assessments should be performed as indicated in the Time and Events Schedule, respectively for the Day 7, Day 10, Day 14, and Day 28 visit.
b. The subject may be discharged after the Day 2 study procedures. Subjects may also remain hospitalized if deemed appropriate by the investigator. Days 3 to 6 assessments are to be performed on a daily basis or as indicated only if the subject is still hospitalized with the exception of administration of study drug dose, mid-turbinate nasal swabs, and subject eCOA, which are to be continued at home. Hospitalization duration will not be extended solely for study purposes. Telephone calls to subjects to facilitate compliance with study procedures between outpatient study visits are permitted.
c. If dose duration is increased to up to 10 days, then all assessments performed on Day 7 will again be performed 1 day (+2 days) after administration of the last MD.
d. Assessments are to be performed once daily or as indicated only if the subject is still hospitalized.
e. Day 28 assessments include only the assessments indicated. Other safety assessments need only be collected if deemed clinically necessary based on an assessment of the subject's safety or as follow-up to an earlier AE.
f. Procedures performed as part of standard of care within approximately 48 hours prior to screening completion (ie, randomization) may be used in determining study eligibility.
g. These assessments are not required per protocol, however, if clinical/safety evaluations are performed as part of routine clinical care while hospitalized, the results of these assessments will be collected in the eCRF for viral, safety, and/or clinical evaluation.
h. Study drug should be given as soon as possible but no later than 4 hours after randomization. Study drug will be given as an LD administered for Dose 1 followed by 9 MDs, to be given at least 8 hours apart and maximum 16 hours apart, with no more than 2 doses per calendar day, for a total of 10 doses over 5 or 6 days. ALS-008176 may be given without regard to food. The date and time of dose administration, the date and time of food intake (limited to the food ingested within 30 minutes before or after study drug administration), and the type of food will be recorded in the eCRF during hospitalization. The date and time of dose administration will be recorded in the electronic device used for eCOA in case the subject is discharged prior to completion of treatment See Attachment 8 for details on collection of food intake information.
i. Upon discharge, subjects will be required to document intake of study drug on the electronic device used for eCOA in a study drug log.
j. An electronic device will be provided to each subject at screening and the investigator/study-site personnel will provide sufficient information to enable the subject to complete the subject eCOA (including RI-PRO, additional questions about health and functioning, and HRQoL [EQ-5D-5L]). The subjects will complete the eCOA once daily throughout the study from screening to Day 28 at approximately the same time each day. If the subject is unable to complete the assessment on the device, the subject's spouse, partner, relative, friend or the investigator/study-site personnel trained on the eCOA device can read the questions and responses aloud to the subject, and enter the subject's responses in the eCOA device on the subject's behalf using the interview administration procedures explained in the eCOA completion guide. For Part 2, the questions will be read from the device for RI-PRO and additional questions about health and functioning, and from a paper form of the questionnaire provided to the caregiver by the site for HRQoL. If in the investigator's opinion, the subject (or the subject's spouse, partner, relative, or friend) is unlikely to reliably enter the information in the eCOA device on a daily basis for the duration of the study, the site will retain the eCOA device upon the

subject's discharge and arrange for the investigator or trained study-site personnel to interview the subject by phone and record the subject's responses in the eCOA device on the subject's behalf each day post discharge to end of follow-up.

k. The assessment on Day 1 must be recorded predose, before the LD. If the screening assessment was performed less than 8 hours prior to LD, the predose assessment does not need to be performed.

l. Clinical evaluation includes, but is not limited to, RSV disease symptoms, oxygen requirement (type, duration, and amount), level of hospital care, duration of hospitalization, respiratory rate, SpO_2, and body temperature.

m. The Katz ADL questionnaire will be completed by the investigator/study-site personnel after interviewing the subject and the data will be entered into the eCRF by the investigator/study-site personnel. The Katz ADL questionnaire will be completed twice at screening to document retrospectively the subject's pre-RSV infection functional status (ie, prior to first signs/symptoms of RSV) and the subject's current functional status (ie, after the occurrence of RSV signs/symptoms). The Katz ADL questionnaire will be completed once daily for the entire duration of hospitalization and on Day 7, Day 10, Day 14, and Day 28 if the subject is discharged.

n. SpO_2 will be assessed Q4h (±30 minutes) while the subject is hospitalized through Day 7. Previous time point should be used to calculate the next measurement window. In case the last SpO_2 assessment on Day 7 was performed after 8 PM, the first SpO_2 assessment on Day 8 should be performed within 8 hours from the last SpO_2 assessment on Day 7. For subjects who remain hospitalized after Day 7, SpO_2 assessment should then continue Q8h (±1 hour) until 24 hours after the cessation of supplemental oxygen. After discharge, SpO_2 will be assessed once on Day 7, Day 10, Day 14, and Day 28.

o. Only to be performed if the test is available at the study site and the clinical condition of the subject allows testing as judged by the investigator.

p. A CPE includes all body systems, height (only at screening), and body weight; a DPE includes respiratory system, nose, ear, throat, facial and neck lymph nodes, and skin examination. A CPE will be performed at screening and Day 28 and a DPE will be performed on Days 1, 2, 7, 10, and 14. Additionally, physical examination findings performed as part of standard of care on Days 8 to 13 will also be collected.

q. Vital signs are defined as SBP, DBP, temperature, respiratory rate, and heart rate. Symptom-directed vital signs will also be performed when deemed appropriate by the investigator or appropriately delegated study team member. Vital signs will be assessed twice daily (preferably at the same times each day, ±30 minutes) for the entire duration of hospitalization. After discharge, vital signs will be assessed once on Day 7, Day 10, Day 14, and Day 28. Additionally, vital signs assessed as part of standard of care on Days 8 to 13 will be collected.

r. Part 1: Triplicate 12-lead ECGs (three 10-s recordings at approximately 60-s intervals) will be collected and analyzed by a central laboratory at screening, on Day 1, on Day 7, on Day 28, and when clinically indicated. On Day 1, triplicate ECGs will be collected at 2 time points: approximately 30 to 60 minutes and 3 to 6 hours after the LD. If an ECG is abnormal at Day 7, an additional ECG should be performed at Day 14. Part 2: a single 12-lead ECG will be collected and analyzed by a central laboratory at screening, on Day 4 (for subjects who remain hospitalized at this time), on Day 28, and when clinically indicated. If discharged earlier than Day 4, the subject needs to have an ECG recorded on the day of discharge. The ECG will be performed 30 minutes to 3 hours after the first dose of study drug of that day. If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, followed by vital signs/oxygen saturation, mid-turbinate nasal swabs, then blood draw.

s. The mid-turbinate nasal swab (if non-intubated) or endotracheal sample (if intubated) taken during screening is placed in 3 mL of transport media and split into several aliquots, which are used to confirm RSV infection locally and centrally, and to assess for viral and bacterial co-infection centrally. From Day 1 to Day 7 and on Day 10, Day 14, and Day 28, 1 mid-turbinate nasal swab (if non-intubated) or 1 mid-turbinate nasal swab and 1 endotracheal sample (if intubated) will be taken per day to assess RSV RNA viral load and resistance and in some cases to assess the infectious virus yields using a plaque assay. Should the study drug duration be increased to up to 10 days (following review of the data by the IDMC), 1 mid-turbinate nasal swab (if non-intubated) or 1 mid-turbinate nasal swab and 1 endotracheal sample (if intubated) will be taken every day up to and including 1 day (+2 days) following the last dose of study drug. The timing of the LD will determine the nasal swab and/or endotracheal sampling times. If the administration of the LD is in the morning, all nasal swabs and/or endotracheal samples will be taken before the morning doses. If the administration of the LD is in the afternoon, all nasal swabs and/or endotracheal samples will be taken before the afternoon doses but after the morning doses. In case of nostril bleeding or irritation during the collection of a mid-turbinate nasal swab, all subsequent nasal swabs will be performed on the contralateral nostril. In case mid-turbinate nasal swabs are collected at home, this should be documented in the eCOA. Wherever possible,

mid-turbinate nasal swabs should be collected by a trained study team member in an inpatient or outpatient (clinic visit) setting. Whenever mid-turbinate nasal swabs cannot be taken by a trained study team member, the subject (or the subject's spouse, partner, relative, or friend) should collect swab specimens after being trained by the investigator/study-site personnel.

t. Leftover mid-turbinate nasal swabs may be used to explore biomarkers (eg proteins including cytokines) at the discretion of the sponsor.

u. Mid-turbinate nasal swab (if non-intubated) or mid-turbinate nasal swab and endotracheal sample (if intubated) must be taken as close as possible to and before the LD on Day 1. If the screening mid-turbinate nasal swab or endotracheal sample was performed less than 8 hours prior to LD, the Day 1 predose sample does not need to be collected.

v. Safety laboratory tests (hematology and biochemistry) will be performed by the local laboratory at screening and during the follow-up phase at Day 7, Day 14, and Day 28. Hematology and biochemistry (Part 2 of the study only) tests will be additionally performed during the treatment phase on Day 2, Day 4, and Day 6 while hospitalized and during the follow-up phase at Day 10. Urinalysis will be performed at Day 1 and during the follow-up phase at Day 7 and Day 14. A urinalysis performed in the context of routine clinical care during the screening period may be used for the baseline urinalysis. If on any other day blood or urine is collected during routine clinical care while hospitalized, the results of these assessments will be collected in the eCRF for safety evaluation. Additional safety samples may also be collected on an ad hoc basis in the event that a safety event arises, at the discretion of the investigator or at the request of the sponsor. Leftover blood samples may be used for exploratory biomarker analyses (eg, proteins including cytokines).

w. Part 1: PK samples should be collected at:
Dose 1 (LD): 0.5 to 1 hour postdose, 2 to 3 hours postdose, and 4 to 6 hours postdose
Dose 2: predose, 0.5 to 1.5 hour postdose, and 3 to 6 hours postdose
Dose 3: if patient has not been discharged, predose (preferable), or random sample
Day of discharge if still on study drug: random sample
Dose 10: if patient has not been discharged, predose (preferable) or random sample
Day 7: random sample at visit
Day 10: random sample at visit
If >10 doses are administered upon IDMC recommendation: prior to the last dose (if feasible)

Part 2: PK samples should be collected at:
Dose 1 (LD): 0.5 to 1 hour postdose, and 2 to 3 hours postdose
Dose 2: predose, and 3 to 6 hours postdose
Dose 3: if patient has not been discharged, predose (preferable), or random sample
Dose 10: if patient has not been discharged, predose (preferable) or random sample
Day 7: random sample at visit
Day 10: random sample at visit
Day of discharge if still on study drug: random sample

The actual dates and times of sample collection must be recorded in the eCRF. When occurring on the same day, safety and biomarker blood samples may be collected at the same time as PK sampling to minimize the number of venipunctures. A predose PK sample is defined as one collected within 0.5 hour (≤30 minutes) prior to the next dose. Additional PK samples may also be collected on an ad hoc basis as a safety assessment in the event that a safety event arises for which an understanding of drug exposure is clinically important, at the discretion of the investigator or at the request of the sponsor.
See Attachment 8 for details on PK sampling and collection of food intake information.

x. Prestudy therapies administered up to 7 days before the first dose of study drug must be recorded at screening. Concomitant therapies must be recorded throughout the study beginning with the start of the first dose of study drug up to the Day 28 visit (±2 days). During hospitalization, concomitant medication will be recorded by the site staff in the eCRF. Upon discharge, subjects will be required to document use of concomitant medication in the electronic device in a medication log, which will serve as basis for recording the concomitant medication in the eCRF by the site staff.

y. All AEs and SAEs will be collected continuously from signing of the ICF onwards until the last follow-up visit (EoS visit). Any clinically significant abnormalities persisting at the EoS/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

z. The ordinal scale will be assessed on the day of the last dose (Day 5/6 [depending on the timing of the LD administration]). In case the subject is discharged before Day 5/6, the subject should be contacted to ask if the subject has returned to usual activities.

ABBREVIATIONS

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-inf}	area under the concentration-time curve from time zero extrapolated to infinite time
AUC_{0-last}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{0-xh}	area under the concentration-time curve from time 0 to x hours after dosing
BCRP	breast cancer resistance protein
BFU-E	burst forming unit-erythroid
CFU-GM	colony forming unit-granulocyte monocyte
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C_{max}	maximum observed or predicted concentration
C_{min}	minimum observed or predicted concentration
COPD	chronic obstructive pulmonary disease
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DLCO	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQoL 5 Dimension 5 level version
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	Investigator's Brochure
IC_{50}	concentration resulting in 50% of the maximum inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
K_i	inhibition constant
LD	loading dose
MD	maintenance dose
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NTP	nucleoside triphosphate
OAT	organic anion transporter
PCR	polymerase chain reaction
PD	pharmacodynamics(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcomes

qRT-PCR	quantitative reverse transcriptase-polymerase chain reaction
QTc	corrected QT
QTcF	QT corrected according to Fridericia's formula
RBC	red blood cell
RI-PRO	respiratory infection patient-reported outcome
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
t_{max}	time to maximum concentration
ULN	upper limit of normal
V_c	central volume of distribution
WBC	white blood cell

DEFINITIONS OF TERMS

Electronic Clinical Outcome Assessment (eCOA)	Includes patient-reported outcomes (PROs) collected on an electronic device (eg. respiratory infection PRO [RI-PRO], additional questions about health and functioning, and health-related quality of life [HRQoL] EuroQoL 5 Dimension [EQ-5D-5L]).

1. INTRODUCTION

Respiratory syncytial virus (RSV) is a ribonucleic acid (RNA) virus and a member of the *Pneumoviridae* family, which also includes human and avian metapneumovirus and murine pneumonia virus. The RSV season occurs during winter months in regions with temperate climates in the Northern and Southern Hemispheres and throughout the year or peaks semiannually in tropical regions.[5,16]

ALS-008176 (also known as JNJ-64041575 or lumicitabine) is an orally administered drug intended for the treatment of children and adults infected with RSV. ALS-008176 is a 3′,5′-bisisobutyrate prodrug of the cytidine nucleoside analog polymerase inhibitor, ALS-008112, and is a replication inhibitor of RSV, which works via a classic chain termination mechanism. Once administered, it is rapidly and efficiently converted by esterases to ALS-008112, which is subsequently converted intracellularly, to the active nucleoside triphosphate (NTP), ALS-008112-5′-triphosphate (ALS-008136). The only major metabolite of ALS-008112 is ALS-008144, which is the inactive uridine analog metabolite. The monoester of ALS-008176, ALS-008206, is a minor metabolite.

Table 2: Investigational Product and its Metabolites

Compound Number	Description
ALS-008176 (JNJ-64041575, lumicitabine)	3’,5’-bisisobutyrate prodrug of ALS-008112
ALS-008112 (JNJ-63549109)	parent nucleoside analog, major metabolite of ALS-008176, inactive
ALS-008206 (JNJ-64412309)	3’-isobutyrate monoester of ALS-008112, minor metabolite, inactive
ALS-008207 (JNJ-64412296)	5’-isobutyrate monoester of ALS-008112, minor metabolite, inactive
ALS-008144 (JNJ-64167896)	uridine analog metabolite of ALS-008112, major metabolite, inactive
ALS-008136 (JNJ-65409136)	5’-triphosphate of ALS-008112 (NTP), intracellular metabolite, active
ALS-008137 (JNJ-65409123)	5’-monophosphate of ALS-008112, intracellular metabolite, inactive

Abbreviation: NTP: nucleoside triphosphate.

Data from an RSV human challenge study, Study ALS-8176-502, have demonstrated that ALS-008176 doses up to a single 750 mg loading dose (LD) followed by nine 500 mg maintenance doses (MDs) resulted in the inhibition of RSV replication with an associated reduction in the signs and symptoms of the RSV infection in healthy subjects, and was well tolerated.[9]

For the most comprehensive nonclinical and clinical information regarding ALS-008176 refer to the latest version of the Investigator’s Brochure (IB) for ALS-008176, and its addenda.[2,3,4,5,16]

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

1.1. Background

This study will evaluate the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics (PK) of orally administered ALS-008176 regimens in adults hospitalized with RSV infection.

Nonclinical Studies

Pharmacologic Profile

The antiviral activity and selectivity of the parent nucleoside analog ALS-008112 and its prodrug, ALS-008176, were evaluated in vitro using a combination of cell-based RSV infectious and subgenomic replicon reporter systems, together with cell-extracted replicase and recombinant RSV polymerase L-P complex. In vivo, ALS-008176 was evaluated in the African Green monkey model of RSV infection.

The major findings as reported in the IB from these studies were:

- When incubated with RSV-infected cells, ALS-008112 and ALS-008176 are selective inhibitors of both RSV laboratory-adapted A and B strains as well as a range of diverse clinical isolates.
- ALS-008112 and ALS-008176 demonstrate selective inhibition of RSV replication in the HeLa cell RSV subgenomic replicon system.
- The ALS-008112-5'-triphosphate (ALS-008136), the active metabolite of the compound, is a selective inhibitor of RSV RNA-dependent polymerase activity with an inhibition constant (K_i) of 0.09 μM.
- After nucleotide incorporation using ALS-008136, no subsequent nucleotide was incorporated at the 3'OH end of the RNA template indicating that ALS-008136 inhibits the RSV polymerase activity by immediate chain termination.
- ALS-008136 is formed in high amounts in A549 lung epithelial cells, primary human nasal and bronchial epithelial cells, and monkey lung, and demonstrates an intracellular half-life ($t_{1/2}$) of approximately 17.6 hours in cell culture (in normal human bronchial epithelial cells) and 29 hours in vivo (in monkey lungs).
- ALS-008112 also inhibited the replication of other respiratory viruses such as parainfluenza-3 and human metapneumovirus.
- Viral resistance to ALS-008112 was mediated by multiple amino acid substitutions (M628L/A789V/L795I/I796V) in the RSV polymerase domain of the RSV L-protein.
- The effect of prophylactic treatment with ALS-008176 on the replication of RSV A2 in the African Green monkey model was studied. At Day 5 postinfection (end of treatment) there was a difference of >4 $\log_{10}$ copies/mL between the RSV RNA viral load titers in bronchoalveolar lavage samples of the vehicle-treated animals compared with those from the ALS-008176-treated animals indicating that ALS-008176 treatment significantly suppressed RSV replication in vivo. However, virus relapse was observed in all animals between Days +5 and +15, but was not associated with the emergence of viral resistance to ALS-8176.
- Inhibition of RSV A2 by ALS-008112 was examined in pairwise combination studies with palivizumab, the RSV fusion inhibitors, BMS-433771 and GS-5806, the non-nucleoside RSV polymerase inhibitors, ALS-028414 and AZ-27, consensus interferon (Infergen®), and ribavirin. These ALS-008112 combinations demonstrated strong synergy, synergy or additive effects. None of the compound interactions demonstrated antagonistic effects.

Toxicology Profile

Once administered, ALS-008176 is rapidly and efficiently converted to ALS-008112. Thus, the toxicity profile of ALS-008176 is primarily driven by ALS-008112.

The major toxicity findings were:

Repeat-dose Toxicity

- Target organ for toxicity in both adult and juvenile rats and dogs was the hematopoietic system, next to an effect on body weight (in rats). The no-observed-adverse-effect level (NOAEL) doses of ALS-008176 and exposure of ALS-008112 are presented in Table 3.

Table 3: NOAEL Doses of ALS-008176 and Exposure of ALS-008112 in Adult and Juvenile Rats and Dogs After Repeated Dosing of ALS-008176

Target Organ	Key Finding	Species/Age Group	Dose (mg/kg bid)	NOAEL (ALS-008112 AUC_{0-24h}) (ng.h/mL)
Hematology	↓ reticulocytes, ↓ red blood cell parameters, reversible	Juvenile rat (PND1-28)[a]	150	93,900[b]
		Juvenile dog (PND7-34)	25	108,228
Bone marrow	Cytological changes in bone marrow cells, ↓ myeloid-to-erythroid ratios, reversible	Adult rat (14 days)	150	53,600
		Adult dog (14 days)	75	192,500

Abbreviations: AUC_{0-24h}: area under the curve from time 0 to 24 hours after dosing; bid: twice daily; NOAEL: no-observed-adverse-effect level; PND: postnatal day.
[a] Effects in rats aged PND21-45 were similar to adult rats.
[b] Estimated on PND28 predose values.

- Following 14 days, 28 days, and 13 weeks of repeated dosing, the hematopoietic changes induced by ALS-008112 in adult animals were reversible.
- No effects on early developmental markers, neurobehavior, respiratory function, bone geometry, bone densitometry, ophthalmological evaluations, or electrocardiograms (ECGs) in juvenile rats (150 mg/kg twice daily; ALS-008112 area under the concentration-time curve from time 0 to 24 hours after dosing [AUC_{0-24h}] of 55,450 ng.h/mL) and dogs (75 mg/kg twice daily; ALS-008112 at AUC_{0-24h} of 258,862 ng.h/mL).

Genotoxicity

- Non-mutagenic (negative Ames test) and no DNA damage (COMET assay; 1,750 mg/kg/day, 3 days) potential for ALS-008176 or its metabolites.
- Increases in structural chromosomal aberrations in human peripheral blood lymphocytes induced by ALS-008112 (≥10 µg/mL). Positive micronucleus test in rats (≥425 mg/kg/day ALS-008176, 3 days) at high exposures of ALS-008112 (AUC_{0-24h} ≥107,983 ng.h/mL). The no-observed-effect level (NOEL) for in vitro chromosomal aberrations was 5 µg/mL ALS-008112 and for in vivo micronucleus induction was a ALS-008112 AUC_{0-24h} of 57,595 ng.h/mL.

- The mechanism of clastogenicity is an indirect, threshold-based mechanism of intracellular nucleoside triphosphate pool disturbances rather than direct DNA reactivity, as described for other nucleoside analog inhibitors in the public domain.
- A maximum average threshold of ALS-008112 exposure in humans has been defined as an $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL. This threshold provides safety margins that are at least 2.5-fold (vs 13-week adult rat study), 2.7-fold (vs 14-day adult rat study), and 4.7-fold (vs 28-day juvenile rat study) lower for adults and infants, respectively, than the lowest NOAEL exposure obtained in nonclinical studies.

Reproductive Toxicity

- The NOAEL for male reproductive toxicity/fertility in rats was 250 mg/kg twice daily (ALS-008112 $AUC_{0\text{-}24h}$ of 165,000 ng.h/mL). Although a slight decrease in corpora lutea and corresponding decrease in implantations and viable embryos was seen at 250 mg/kg twice daily in females, it did not have any overall impact on female fertility or in utero survival. Therefore, the NOAEL for female reproductive toxicity as well as early embryonic toxicity was considered to be 250 mg/kg bid (ALS-008112 $AUC_{0\text{-}24h}$ of 193,000 ng.h/mL).
- The effects of ALS-008176 on developmental and reproductive parameters were a decrease in fetal weight with concomitant skeletal developmental variations in rats at 400 mg/kg twice daily and lower litter proportion of viable fetuses due to an increase in post-implantation losses in rabbits at ≥20 mg/kg twice daily, with no teratogenic effects in fetuses in either rats or rabbits. The NOAEL for maternal toxicity and embryo-fetal development in rats was 125 mg/kg twice daily (ALS-008112 maximum plasma concentration [C_{max}] of 11,400 ng/mL and $AUC_{0\text{-}24h}$ of 87,800 ng.h/mL). The NOAEL for embryo-fetal development in rabbits was 10 mg/kg twice daily (ALS-008112 $AUC_{0\text{-}24h}$ of 8,220 ng.h/mL) and the maternal NOAEL in rabbits was 20 mg/kg twice daily.

Other Toxicity

- No measurably cytotoxicity of ALS-008112 (100 µM, 3 days) in the human epithelial type 2 (HEp-2) and the Huh-7 cell lines.

Pharmacokinetic and Metabolism Profile

The major nonclinical pharmacokinetic (PK) and metabolism findings were:

- The prodrug ALS-008176 was well absorbed after oral administration and rapidly and efficiently converted to the parent nucleoside analog ALS-008112 by esterases (mainly carboxylesterase 2). Plasma exposures of ALS-008112 were comparable between adult and juvenile animals at the same dose levels. The uridine metabolite ALS-008144 was a major circulating metabolite (especially in monkeys).
- Food slowed down the rate of oral absorption (lowered C_{max} values) of ALS-008176, but did not change the extent of oral absorption (no change in area under the curve [AUC]) in monkeys.
- The oral bioavailability, in terms of exposure of the parent nucleoside analog ALS-008112, was 44% in dog and monkey.

- Inside cells ALS-008112 is extensively phosphorylated. In lung, high levels of the monophosphate ALS-008137 and especially the active triphosphate ALS-008136 were measured.
- Cytochrome P (CYP) enzymes play a minor role in ALS-008176 metabolism. No other relevant inhibition nor induction of CYP enzymes by ALS-008176, ALS-008112 or other metabolites was observed.
- ALS-008176 is a substrate of P-glycoprotein (P-gp) at 0.5 µM and higher, with no P-gp saturation measured up to 150 µM. ALS-008176 is not an inhibitor of P-gp. ALS-008112 appears to be a P-gp substrate at 2 µM, but not at 50 µM and higher concentrations, and it is not an inhibitor of P-gp. ALS-008144 is neither a substrate nor inhibitor of P-gp. ALS-008176, but not ALS-008112 and ALS-008144, might be weak inhibitors of organic anion-transporting polypeptide (OATP) 1B1/1B3, but none of them are substrates of these OATP1B transporters. Data indicated that ALS-008112 and ALS-008144 are neither substrates nor inhibitors of organic cation transporter (OCT) 2, organic anion transporter (OAT) 1, and bile salt export pump (BSEP). There is no clear indication that ALS-008176 and ALS-008112 are substrates of breast cancer resistance protein (BCRP). ALS-008144 is no BCRP substrate. None of them are inhibitors of BCRP. ALS-008112 is a substrate but not an inhibitor of OAT3 (Ki >258 µM). ALS-008144 is not a substrate or inhibitor of OAT3
- Based on the in vitro data, ALS-008176 and its major metabolites are predicted to have a low potential for CYP- and transporter-mediated drug-drug interactions, with the exception of OAT3 inhibitors and potential exception of P-gp inhibitors and inducers.

Clinical Studies

Human Pharmacokinetics

Single-dose PK in healthy adult subjects was characterized for single doses of ALS-008176 ranging from 40 to 750 mg in a suspension formulation (Study ALS-8176-501) and for single doses of 1,500 and 3,000 mg in a tablet formulation (Study 64041575RSV1003) administered orally to healthy adult subjects in the fasted state. ALS-008176 was rapidly converted to ALS-008112. The only other major metabolite measurable in plasma was ALS-008144, the inactive uridine metabolite of ALS-008112. The majority of the plasma concentrations of ALS-008112 generally decreased to low levels within 6 to 12 hours postdose, indicating rapid and extensive distribution of this metabolite. With increasing doses of ALS-008176 (40 to 3,000 mg), the C_{max} of ALS-008112 increased in a less than dose proportional manner, while the C_{max} of ALS-008144 and the AUCs of both metabolites increased close to dose proportionally. The plasma PK profile of the metabolite, ALS-008144, was similar to that of ALS-008112 and exposure (area under the concentration-time curve from time zero to the time of the last quantifiable concentration [$AUC_{0\text{-last}}$]) was approximately 20% to 54% of that of ALS-008112.

Food effect was assessed for several ALS-008176 suspension and tablet formulations (Study ALS-8176-501: suspension at 250-mg dose, Study ALS-8176-509: 500-mg tablet, and Study 64041575RSV1005: suspension at 240-mg dose and 250-mg tablet). Intake of a single 240-mg oral dose of the ALS-008176 suspension used in Study 64041575RSV2004 with a high fat, high calorie meal lowered ALS-008112 C_{max} by 57% as compared with the fasted state,

without affecting the ALS-008112 area under the concentration-time curve (Treatment B and C in Study 64041575RSV1005). Administration of ALS-008176 500-mg tablet used in Study 64041575RSV2003 with a high fat, high calorie meal had a minor effect on ALS-008112 area under the concentration-time curve and C_{max}, as compared to the fasted state (Formulation A in Study ALS-8176-509).

Study ALS-8176-504 determined the absolute bioavailability of ALS-008112 and mass balance of ALS-008176 in healthy adult subjects. Following oral administration of a 375 mg ^{14}C-ALS-008176 solution, 84% of the total administered radioactive dose was recovered in the urine and feces during the 312-hour collection period. Approximately half of the administered dose was recovered within the first 24 hours. Approximately two-thirds of the total radioactivity was recovered in the urine suggesting renal elimination is the major route of elimination for the prodrug and its metabolites. Metabolite profiling and identification confirmed that ALS-008112 and ALS-008144 are the 2 major metabolites in plasma, urine, and/or feces. The absolute oral bioavailability of an oral dose of 500-mg of ALS-008176, measured by the formation of the parent nucleoside analog, ALS-008112 ($AUC_{0\text{-last}}$), was determined to be approximately 60%.

Study 64041575RSV1006 investigated the PK of ALS-008176 after a single oral dose of 1,000 mg in adult subjects with various degrees of impaired renal function. Overall, based on the geometric mean ratios, C_{max} of ALS-008112 was similar in subjects with impaired renal function compared to subjects with normal renal function, and $AUC_{0\text{-last}}$ and area under the concentration-time curve from time zero extrapolated to infinite time ($AUC_{0\text{-inf}}$) increased with a decrease in renal function (Table 4).

Table 4: Pharmacokinetic Parameters of ALS-008112 Following a Single Oral Dose of 1,000 mg ALS-008176 in Subjects With Different Degrees of Renal Function

Pharmacokinetic Parameter of ALS-008112	Normal renal function	Mild impaired renal function	Moderate impaired renal function	Severe impaired renal function	End-stage renal disease
n[a]	14	6[a]	6	6[b]	6[a]
C_{max} (ng/mL)	3,258	2,800	4,108	3,721	3,682
$AUC_{0\text{-last}}$ (ng.h/mL)	11,659	12,905	18,260	19,105	25,335
$AUC_{0\text{-inf}}$ (ng.h/mL)	12,438	14,455	19,550	21,086	30,410

Abbreviations: $AUC_{0\text{-last}}$: area under the concentration-time curve from time zero to the time of the last quantifiable concentration; $AUC_{0\text{-inf}}$: area under the concentration-time curve from time zero extrapolated to infinite time; C_{max}: maximum plasma concentration; eGFR: estimated glomerular filtration rate.
Normal renal function: eGFR ≥90 mL/min; Mild renal impairment: eGFR ≥60 to <90 mL/min; Moderate renal impairment: eGFR ≥30 to <60 mL/min; Severe renal impairment: eGFR ≥15 to <30 mL/min; End-stage renal disease: eGFR <15 mL/min if not on hemodialysis or requiring hemodialysis treatment for ≥3 months before screening if on hemodialysis
[a] n=5 for $AUC_{0\text{-inf}}$
[b] n=5 for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$

Multiple dose PK was characterized in healthy adult subjects in Study ALS-8176-501, in healthy adult subjects challenged with RSV in Study ALS-8176-502, and in hospitalized adult subjects with RSV infection in Part 1 of Study 64041575RSV2003. Following multiple oral doses of ALS-008176 in healthy adult subjects in Study ALS-8176-501, including 2 loading doses (LDs) up to 750 mg on Day 1 followed by administration of maintenance doses (MDs) up to 500 mg up

to 13 days every 12 hours (Q12h), the plasma profiles of ALS-008112 and ALS-008144 were similar to those obtained following single doses of ALS-008176. Accumulation of either ALS-008112 or ALS-008144 was insignificant after 5 days of dosing. Steady-state minimum observed analyte concentration (C_{min}) of ALS-008112 was reached by the second dose and minimal changes in C_{min} concentrations were noted between Days 1 and 5 or 14. In general, the plasma profiles for ALS-008112 following the PM dose were lower than following the AM dose. Study ALS-8176-502 was an RSV challenge study in healthy adult subjects. Subjects received 5-day dosing regimens of ALS-008176 as an oral suspension. The 3 dose regimens were: 375 mg Q12h (n=11), 750 mg LD/500 mg MD Q12h (n=14), and 750 mg LD/150 mg MD Q12h (n=19). Intensive PK samples were evaluated on Days 1 and 5 of the study and the highest mean plasma $AUC_{0\text{-}24h}$ for ALS-008112 was 10,794 ng.h/mL on Day 5 for the 750 mg LD/500 mg MD group. There was no difference between the average exposures after oral dosing of ALS-008176 in healthy adult subjects in Study ALS-8176-501 as compared with healthy adult subjects challenged with RSV in Study ALS-8176-502. The primary objective of Part 1 of Study 64041575RSV2003 was to characterize the PK and to confirm the population pharmacokinetic (popPK) model derived from healthy subjects in hospitalized adults who are infected with RSV. The PK data used in the analysis for Part 1 of this study were obtained from 15 subjects dosed with 750 mg LD/250 mg MD ALS-008176. Individual concentrations and clearance, C_{max}, C_{trough} and $AUC_{0\text{-}24h}$ were reliably estimated. The mean model $AUC_{0\text{-}24h}$ was 9,872 ng.h/mL on Day 1 and 7,551 ng.h/mL on Day 5, well below the average limit of exposure set at $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL.

Multiple dose PK was also characterized in hospitalized pediatric subjects with RSV infection in Study ALS-8176-503. In the multiple ascending dose (MAD) part, RSV-infected infants received a LD (up to 60 mg/kg) followed by 5-day MDs (twice daily) of ALS-008176 (up to 40 mg/kg). The mean plasma ALS-008112 $AUC_{0\text{-}24h}$ increased slightly less than dose proportionally on Day 1 from 1,210 ng.h/mL for the 4.1 mg/kg LD/1.37 mg/kg MD regimen to 15,420 ng.h/mL for the 60 mg/kg LD/40 mg/kg MD regimen.

Based on an integrated popPK approach, race (ie, Caucasian versus Asian, including Japanese) does not affect exposures to ALS-008112, and body weight and creatinine clearance are important covariates on the clearance of ALS-008112. Additionally, lumicitabine formulation as a suspension or tablet, and intake of food are important covariates on the absorption and its between-subject variability.

Study 64041575RSV1002 investigated the potential PK effect of probenecid (chosen as a clinically relevant and strong OAT3 inhibitor) on ALS-008112. Based on the LSmeans ratios, the ALS-008112 C_{max} and $AUC_{0\text{-}last}$ were 1.28-fold and 1.75-fold higher, respectively, after coadministration of probenecid with ALS-008176 compared to the administration of ALS-008176 alone.

Efficacy/Safety Studies

ALS-008176 demonstrated similar in vitro antiviral activity against the closely related *Pneumoviridae* virus family members hMPV and RSV.[16] Currently, no studies evaluating the

efficacy of ALS-008176 for the treatment of hMPV infection in hospitalized adult subject are available. Information from RSV-related studies is therefore reported. Based on the in vitro results, the safety profile of ALS-008176 is expected to be similar in hospitalized adult subjects infected with RSV and in those infected with hMPV.

The efficacy of ALS-008176 in naturally RSV-infected subjects has not yet been demonstrated; however, it has been assessed in healthy adult subjects infected with RSV in a human challenge model (Study ALS-8176-502). In this study, 62 subjects were administered a nasal inoculation of RSV-A Memphis 37b virus on Study Day 0 and then monitored from Study Day 2 to 5 for the presence of RSV infection using a qualitative polymerase chain reaction (PCR) assay in nasal washes collected twice daily. Twelve hours after RSV detection by qualitative PCR, or at Day 6 for subjects who did not have an RSV positive result by qualitative PCR by the evening of Study Day 5, subjects were randomized and administered the first dose of study drug. Subjects were randomized to receive 5 days treatment with placebo or with 1 of the 3 lumicitabine dosing regimens: 750 mg LD/500 mg MD Q12h, 750 mg LD/150 mg MD Q12h, or 375 mg Q12h. Respiratory syncytial virus viral load was measured using a quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) assay in nasal washes collected twice daily from Study Day 2 through 12 and once daily on Study Day 16 and 28. Data from this study demonstrate that MDs of 150 and 500 mg of ALS-008176, following a 750 mg LD, resulted in rapid, substantial declines in RSV viral load with an accompanying comparable improvement in signs and symptoms of RSV infection compared with placebo-treated subjects. There was a statistically significant difference in RSV AUC in subjects treated with 375 mg Q12h compared with placebo but the effect was more pronounced when the regimens included a LD.

For Study ALS-8176-503 in hospitalized pediatric subjects with RSV infection, RSV viral load data are available from a snapshot analysis for the 40 mg/kg LD/20 mg/kg MD cohort (N=12 lumicitabine and N=5 placebo) and the 60 mg/kg LD/40 mg/kg MD cohort (N=5 lumicitabine and N=0 placebo). A steeper slope of RSV RNA decline is observed in both active treatment arms compared to the placebo arm during the first 3 days of treatment, with at Day 3 a mean change from baseline in RSV RNA of -2.6 $\log_{10}$ PFUe/mL in both the active treatment arms compared to -1.2 $\log_{10}$ PFUe/mL in the placebo arm. In the 60 mg/kg LD/40 mg/kg MD treatment arm the mean viral load appeared to increase again at Day 4 and 5; however, the number of subjects with RSV RNA data available in this analysis is limited, hence conclusions cannot be made.

Safety and Tolerability

Healthy Adult Subjects

Data from 8 Phase 1/2a studies (ALS-8176-501, ALS-8176-502, ALS-8176-504, ALS-8176-509, 64041575RSV1001 [ALS-8176-511], 64041575RSV1002, 64041575RSV1003, and 64041575RSV1005), in healthy adult subjects (N=300, for 447 exposures to ALS-008176), indicate that ALS-008176 was well tolerated and that no safety concerns were identified, after receiving ALS-008176 as single doses up to 3,000 mg or as multiple doses up to 750 mg twice daily on Day 1 followed by up to 500 mg Q12h MDs for up to 13 days. No deaths, serious

adverse events (SAEs) or adverse events (AEs) leading to study drug discontinuation considered to be at least possibly related to ALS-008176 reported. All AEs were mild or moderate in severity, except for 3 events, all of which were severe. Two of these severe events were asymptomatic laboratory abnormalities (increased alanine aminotransferase [ALT] and increased blood creatine phosphokinase) and occurred in Study ALS-8176-502; neither event was considered related to ALS-008176. The third severe AE (increased cholesterol) occurred in Study 64041575RSV1001 (ALS-8176-511; single ascending dose [SAD] study in healthy Japanese adult subjects) on Day 14 after the subject received a single oral dose of ALS-008176 (750 mg) on Day 1 and was considered possibly related to ALS-008176. Among healthy adult subjects receiving multiple doses of ALS-008176, the most commonly reported AEs (ie, ≥2% of subjects in any of the treatment groups) that occurred more often in ALS-008176-treated versus placebo-treated subjects were: epistaxis, ALT increased, headache, oropharyngeal pain, platelet count decreased, and upper respiratory tract infection. No clinically concerning findings for any laboratory parameter were reported.

No prolongation of the QT interval corrected for heart rate according to Fridericia's formula (QTcF) of clinical or regulatory concern was noted in Study 64041575RSV1003.

Hospitalized Adult Subjects with RSV Infection

Data is available from 2 Phase 2a/b studies (ALS-8176-510 and 64041575RSV2003) in hospitalized adult subjects with RSV infection.

A total of 9 subjects were enrolled in Study ALS-8176-510, of which 6 subjects received ALS-008176 as a single 750 mg LD followed by 500 mg MDs twice daily for 5 days. All AEs were mild or moderate in severity, apart from one non-serious Grade 4 hematologic AE (neutropenia, laboratory Grade 4) reported in an adult hospitalized subject with RSV infection. The subject had a relevant past medical history including anxiety disorder, chronic obstructive pulmonary disease, depression, and past infections including cellulitis, pneumonia, and urinary tract infection. Some of the subject's concomitant medications could be associated with neutropenia, including acetylsalicylic acid, augmentin, and metoprolol. The event started approximately 23 days after the last dose of ALS-008176 (750 mg LD/500 mg MD twice daily) and was considered possibly related to ALS-008176 by the investigator. One subject in the ALS-008176 group had an SAE of abdominal pain that was considered not related to the study drug. Enrollment in this study was stopped, as it was decided to perform a Phase 2b dose-finding study (64041575RSV2003) instead of a study with a single dose level of ALS-008176.

The Phase 2b Study 64041575RSV2003 was initially designed as a 1-part study to investigate the dose-response relationship of a ALS-008176 dose regimen of 750 mg LD/250 mg MD twice daily and 1,000 mg LD/500 mg MD bid. A Grade 3 SAE of pancytopenia (laboratory Grade 4) that started 2 days after the last dose of ALS-008176 (1,000 mg LD/500 mg MD twice daily) was reported in an adult subject with a medical history of pneumonia, bronchiectasis, anemia, emaciation, and non-tuberculous mycobacteriosis. The event was considered probably related to ALS-008176 by the investigator. This subject had a decreased renal function and concomitant medications that could decrease the renal clearance of lumicitabine, and was found to have

ALS-008112 plasma exposures (Day 1 AUC_{0-24h}=37,400 ng.h/mL) higher than predicted by the initial popPK model. Consequently, the study was temporarily halted (with N=2, 1 subject on ALS-008176 and 1 subject on placebo, further defined as Part 0), and adapted into a 2-part study. Part 1 of Study 64041575RSV2003 was created to characterize the PK in the low-dose arm of 750 mg LD/250 mg MD ALS-008176, to confirm the popPK model derived from healthy volunteers in hospitalized adults with RSV infection, and to more clearly define the study eligibility criteria to ensure subject safety. Furthermore, the safety and tolerability of this regimen was investigated before proceeding to Part 2 of the study which includes the high-dose arm of 1,000 mg LD/500 mg MD ALS-008176.

As of 02 January 2018, 24 subjects had been randomized in Part 1 of Study 64041575RSV2003 (15 on ALS-008176 750 mg LD/250 mg MD twice daily and 9 on placebo). Safety analysis was performed on data collected from these subjects up to 16 January 2018, including the subject on placebo from Part 0 of the study, resulting in a safety set of 25 subjects. The subject treated with ALS-008176 in Part 0 was not included in the analysis due to the different dose and the different inclusion criteria used in Part 1. All AEs were considered mild to moderate. Adverse events reported in at least 12% of subjects in any group were chest pain (muscular), myalgia, rash, headache, ALT increased, hepatic function abnormal, and insomnia. Two subjects in the ALS-008176 group discontinued treatment due to an AE (rash [1 subject] and alanine aminotransferase increased [Grade 3 elevated ALT, 1 subject, concomitant to a Grade 1 elevation in aspartate aminotransferase (AST)]), which were considered mild in nature in both cases. The elevations in ALT and AST were isolated, reversible, asymptomatic, and not associated with concomitant elevations in bilirubin. All AEs resolved during the study period and no severe grade AEs or fatal events were reported. No AEs with regards to neutrophils or other laboratory hematologic parameters, and no cases of graded neutropenia were observed. One subject in both treatment groups had an SAE in the follow-up period, considered not related to study medications (chronic obstructive pulmonary disease [COPD]) for the subject on ALS-008176, and thermal burn and cardiac failure for the subject on placebo).

Hospitalized Pediatric Subjects with RSV Infection

Data is available from 1 Phase 1b first-in-infant study (ALS-8176-503) and 1 Phase 2b study (64041575RSV2004) in hospitalized pediatric subjects with RSV infection. The clinical phase of Study ALS-8176-503 has been completed, but the database has not yet been locked.

Seventy pediatric subjects were treated in the SAD part of Study ALS-8176-503. Fifty-three subjects received single doses of ALS-008176 up to 25 mg/kg and 17 subjects received placebo. All AEs were of mild or moderate severity, except for 1 ≥Grade 3 SAE of bacterial pneumonia which was considered unrelated to the study drug.

In the MAD part of Study ALS-8176-503, 111 pediatric subjects were treated, of which 78 received multiple doses of ALS-008176 up to a 60 mg/kg LD followed by 40 mg/kg MDs twice daily, and 33 subjects received placebo twice daily. All AEs were of mild or moderate severity, except for 6 Grade ≥3 AEs of neutropenia (N=2 Grade 3 and N=4 Grade 4), 1 Grade 3 AE of respiratory failure, and 1 Grade 3 AE of anemia. Four SAEs were reported: lymphadenitis,

neutropenia, bronchiolitis, and respiratory failure. Only the Grade 4 SAE of neutropenia (laboratory Grade 4) reported within 17 hours after the first dose of ALS-008176 (40 mg/kg LD/20 mg/kg MD twice daily) was considered possibly related to the study drug, and resulted in premature discontinuation of the study drug after the second MD. The subject experiencing a Grade 3 SAE of respiratory failure presented also a Grade 2 bacterial pneumonia, and was discontinued from the study on Day 2.

In Study 64041575RSV2004, a Grade 4 SAE of febrile neutropenia (laboratory Grade 4) that started 1 day after the last dose of study treatment was reported in a pediatric subject. The event was considered possibly related to the study drug by the investigator.

1.2. Rationale for the Study

RSV is associated with considerable morbidity and mortality, particularly at the extremes of age (ie, infants and elderly). In the United States alone, among patients >65 years of age, 177,000 hospitalizations and approximately 14,000 deaths per year are attributable to RSV infection.[7] In other countries, the 60-day mortality rate for adults hospitalized with RSV infection has been observed to be as high as 13.8%.[14] There are currently no approved treatments or vaccines to prevent RSV infection in adults. As such, there is a significant unmet medical need for an RSV therapeutic.

This study is designed to determine the antiviral activity, clinical outcomes, safety, tolerability, and PK of multiple ALS-008176 dosing regimens in a population of hospitalized adults naturally infected with RSV. The study will be performed in 2 parts. In Part 1, the PK will be characterized in the low-dose arm of 750 mg LD/250 mg MD ALS-008176. Furthermore, the safety and tolerability of this regimen will be investigated before proceeding to Part 2 of the study which will include the high-dose arm of 1,000 mg LD/500 mg MD ALS-008176. In Part 2, the dose-response relationship of the 750 mg LD/250 mg MD and the 1,000 mg LD/500 mg MD ALS-008176 dosing regimens on antiviral activity will be evaluated. The results of this study will assist in determining the design for subsequent studies in a similar RSV-infected adult population.

Note that, as per Amendment 2, the study will be performed in 2 parts. The 2 subjects (1 on ALS-008176 and 1 on placebo) that were enrolled before the study was temporarily halted, are defined as Part 0. For details, refer to Section 1.1 Background, page 42.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

For Part 1:

The primary objective is to characterize the PK and to confirm the popPK model derived from healthy volunteers in hospitalized adults who are infected with RSV.

For Part 2:

The primary objective is to determine in hospitalized adults who are infected with RSV the dose-response relationship of multiple regimens of ALS-008176 on antiviral activity based on nasal RSV shedding using qRT-PCR assay.

Secondary Objectives

The secondary objectives for Part 1 and Part 2 are to determine in hospitalized adults who are infected with RSV:

- The safety and tolerability of ALS-008176.
- The impact of ALS-008176 on the clinical course of RSV infection including:
  - Duration of hospital stay.
  - Duration of supplemental oxygen.
  - Evolution of Activities of Daily Living (ADL) as assessed by Katz ADL score.
  - Time to clinical stability.
  - Improvement on the ordinal scale.
  - Rate of mortality and complications.
- The antiviral activity based on nasal RSV shedding using qRT-PCR assay (secondary for Part 1 only) and the time to cessation of nasal RSV shedding.
- The impact of ALS-008176 on the emergence of resistant strains of RSV.
- The PK of ALS-008112 and ALS-008144 (and other metabolites, if applicable) in plasma.
- The relationship between the PK and pharmacodynamics (PD; antiviral activity, clinical symptoms, and selected safety parameters) after single (LD) and repeated oral dosing (MD) of ALS-008176.

Exploratory Objectives

The exploratory objectives for Part 1 and Part 2 are to evaluate in hospitalized adults who are infected with RSV:

- The relationship between viral kinetics and clinical outcome, including the relationship between RSV RNA viral load and:
  - Oxygen supplementation.
  - Duration of hospitalization.
  - Katz ADL score.
  - Clinical stability.
- The impact of the baseline viral subtype and genotype on the antiviral activity.
- Onset of complications after initiation of treatment.

- The impact of ALS-008176 on the clinical course of RSV during and following hospitalization as assessed by the subject in the electronic Clinical Outcome Assessment (eCOA) using various scoring systems.
- The impact of RSV and its treatment on health-related quality of life (HRQoL) as assessed by the subject in the eCOA.
- The relationship between the Katz ADL score and the subject eCOA responses.
- Medical resource utilization to manage subjects.
- The comparison of the RSV RNA viral loads measured in mid-turbinate nasal swabs and endotracheal samples from intubated subjects.
- To explore the evolution of diffusing capacity of the lung for carbon monoxide (DLCO) and spirometry in subjects hospitalized with RSV infection.

Additionally, the impact of ALS-008176 on the infectious viral load may be evaluated using a quantitative culture of RSV (plaque assay) on a selected number of subjects and samples (mid-turbinate nasal swabs [if non-intubated] or mid-turbinate nasal swabs and endotracheal samples [if intubated]) at the sponsor's discretion.

2.1.2. Endpoints

Primary Endpoints

For Part 1:

The primary endpoint is the PK of ALS-008112 and ALS-008144 (and other metabolites, if applicable) in plasma.

For Part 2:

The primary endpoint is RSV RNA viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) AUC from immediately prior to first dose of study drug (baseline) until Day 7.

Secondary Endpoints

The secondary endpoints for Part 1 and Part 2 are:

- Safety/tolerability including AEs, physical examinations, vital signs, ECGs, and clinical laboratory results
- RSV clinical course endpoints:
  - Length of hospital stay from admission to discharge and from study treatment initiation to discharge.
  - Length of hospital stay from admission to readiness for discharge and from study treatment initiation to readiness for discharge, with readiness for discharge defined by the investigator.
  - Need for and duration of intensive care unit (ICU) stay.
  - Need for and duration of supplemental oxygen (regardless of method used).

  - Number of hours until peripheral capillary oxygen saturation (SpO_2) ≥93% on room air among subjects who were not on supplemental oxygen prior to the onset of respiratory symptoms.
  - Respiratory rate, SpO_2, and body temperature return to pre-RSV disease level.
  - Need for and duration of noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).
  - Time to return to pre-RSV functional status (Katz ADL score).
  - Need for hydration and feeding by IV catheter/nasogastric tube.
  - Time to clinical stability defined as the time at which the following criteria are all met:
    - normalization of blood oxygen level (return to baseline; by pulse oximetry) without requirement of supplemental oxygen beyond baseline level
    - normalization of oral feeding
    - normalization of respiratory rate
    - normalization of heart rate
  - Improvement on the ordinal scale.
  - All-cause mortality.
- RSV RNA viral load as measured by qRT-PCR of the mid-turbinate nasal swab specimens which will be used to determine the following:
  - Viral load over time.
  - Peak viral load, time to peak viral load, rate of decline of viral load, and time to RSV RNA being undetectable.
  - Proportion of subjects with undetectable viral load at each time point.
  - The RSV RNA viral load AUC from immediately prior to first dose of study drug (baseline) until Day 7 (secondary for Part 1 only).
  - RSV RNA viral load AUC from immediately prior to first dose of study drug (baseline) until Day 10 and until Day 14.
  - RSV RNA viral load AUC in subjects assigned to a longer dosing duration, if dosing duration is increased by the IDMC, from baseline until 1 day after the last dose of study drug (Part 2 only).
- Sequence changes (postbaseline) in the RSV polymerase L-gene and other regions (only if no mutations are seen in the L-gene) of the RSV genome compared with baseline sequences.
- Population-derived PK parameters of ALS-008112.

Exploratory Endpoints

The exploratory endpoints for Part 1 and Part 2 are:

- The amount of:
  - Supplemental oxygen above pre-RSV disease level (regardless of method used) from study treatment initiation to Day 7.

    NOTE: If the dosing duration is increased by the IDMC to up to 10 days, supplemental oxygen above pre-RSV disease level will be measured from treatment initiation until 1 day after the last dose of study drug.
  - Oxygen delivered by noninvasive ventilator support (eg, continuous positive airway pressure) and/or invasive ventilator support (eg, endotracheal-mechanical ventilation or mechanical ventilation via tracheostomy).
  - Subjects (proportion) who started antibiotic use after the first dose of the study drug.
- Disease status and presence of complications with onset after treatment initiation:
  - Bacterial superinfections reported as AEs (eg, pneumonia, acute otitis media, sinusitis, bronchitis, bacteremia).
  - Exacerbations of underlying pulmonary disease (eg, asthma, chronic obstructive pulmonary disease).
  - Cardiovascular and cerebrovascular events (eg, myocardial infarction, congestive heart failure exacerbation, arrhythmia, stroke).
  - Respiratory failure.
  - *Clostridium difficile* associated diarrhea.
  - Other RSV-related complications.
- Duration and severity of signs and symptoms of RSV infection as assessed by the respiratory infection patient-reported outcome (RI-PRO) questionnaire and additional questions about health and functioning completed by the subject in the eCOA.
- HRQoL assessed by the EuroQoL 5 Dimension 5 level version (EQ-5D-5L) completed by the subject in the eCOA.
- Hospital readmission for respiratory reasons up to the Day 28 follow-up visit.
- Medical resource utilization.
- RSV RNA viral load (AUC) as measured by qRT-PCR of mid-turbinate nasal swabs and endotracheal samples in intubated subjects.
- Lung function measured by the DLCO and spirometry test.
- RSV infectious viral load as measured using a quantitative viral culture (plaque assay).

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

For Part 1, no formal hypothesis is specified. Part 1 is intended to characterize the PK in the low-dose arm of 750 mg LD/250 mg MD ALS-008176 and to confirm the popPK model derived from healthy volunteers in hospitalized adult subjects infected with RSV. Furthermore, the safety and tolerability of this regimen will be investigated before proceeding to Part 2 of the study which will include the high-dose arm of 1,000 mg LD/500 mg MD ALS-008176.

For Part 2, the primary hypothesis is that there is a positive dose-response relationship of active treatment on the average RSV RNA viral load AUC with the average AUC on at least 1 of the active treatments being lower than the average AUC on placebo.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-finding study of ALS-008176 in hospitalized adults of ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) who are infected with RSV. The study will be performed in 2 parts.[a]

Part 1

A target of approximately 24 subjects with a maximum of 36 subjects will be randomized in a 1:2 ratio to Regimen A or B:

- Regimen A (placebo): a single LD (Dose 1) followed by 9 MDs (Doses 2 to 10) of matching placebo, administered twice daily.
- Regimen B (low-dose ALS-008176): a single 750 mg LD (Dose 1) followed by nine 250 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.

The IDMC will review the safety and PK data after approximately 12 subjects have completed treatment as per the IDMC charter. When approximately 24 subjects have completed the Day 14 follow-up visit, an unblinded primary analysis will be performed by the sponsor, for review by the IDMC. Further enrollment in this part of the study up to 36 subjects may continue while the data are being analyzed. Once all data for Part 1 are collected and the database locked, the sponsor may perform an unblinded, secondary analysis on the full dataset of Part 1, to support clinical development.

[a] Note that, as per Amendment 2, the study will be performed in 2 parts. The 2 subjects (1 on ALS-008176 and 1 on placebo) that were enrolled before the study was temporarily halted, are defined as Part 0. For details, refer to Section 1.1 Background, page 41.

Part 2

A target of approximately 90 subjects will be randomized in a 1:1:1 ratio to Regimen A, B, or C with approximately 30 subjects planned per treatment regimen:

- Regimen A (placebo): a single LD (Dose 1) followed by 9 MDs (Doses 2 to 10) of matching placebo, administered twice daily.
- Regimen B (low-dose ALS-008176): a single 750 mg LD (Dose 1) followed by nine 250 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.
- Regimen C (high-dose ALS-008176): a single 1,000 mg LD (Dose 1) followed by nine 500 mg MDs (Doses 2 to 10) of ALS-008176, administered twice daily.

Each part of the study will be conducted in 3 phases: a screening phase, a treatment phase from Day 1 to Day 5/6 (depending on the timing of the LD administration), and a follow-up phase for a total of 28 days post randomization. Subjects will have assessments completed during hospitalization and at the Day 7, Day 10, Day 14, and Day 28 visits. Depending on discharge date, assessments will be completed either while hospitalized or during outpatient visits. For hospitalized subjects additional assessments are done as per the Time and Events Schedule. The duration of the subject's participation will be approximately 28 days, screening period not included.

Assessments during the study will include the antiviral activity, measured by RSV RNA viral load using a qRT-PCR assay as well as an evaluation of the clinical course of RSV infection as assessed by the clinician and an evaluation of RSV disease-related signs and symptoms and HRQoL as assessed by the subject. Safety and tolerability, including AEs, laboratory assessments, ECGs, physical examination, and vital signs will be assessed throughout the study from signing of the informed consent form (ICF) until the subject's last study-related activity.

Pharmacokinetic assessments will be performed using a popPK model. Intensive PK sampling in Part 1 of this study will be used to update and confirm the popPK model that was developed based on the data from healthy volunteers. Based on the PK data from hospitalized adult subjects infected with RSV from Part 1 of this study, the PK sampling for Part 2 was optimized. The popPK model may be further modified or adapted as needed.

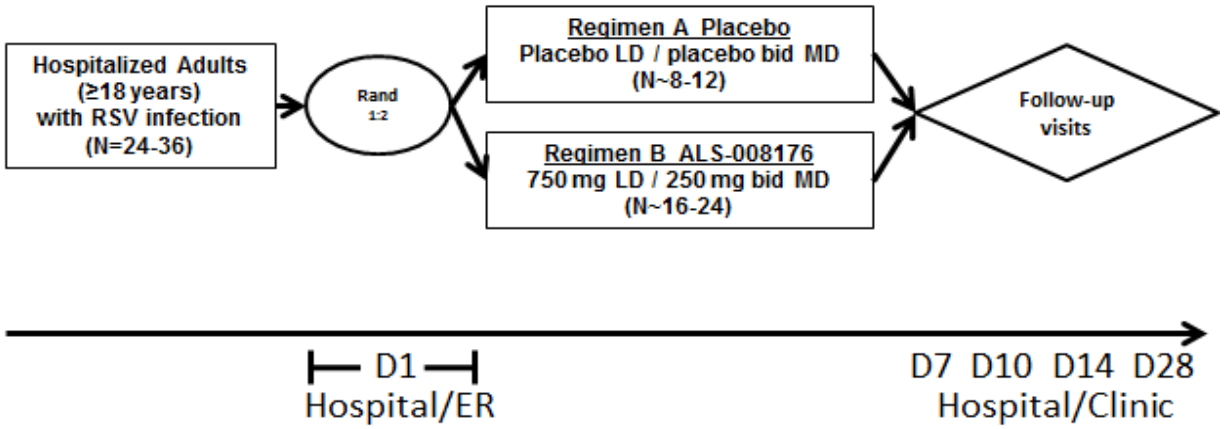
Viral sequencing analysis will be performed to identify preexisting sequence polymorphisms, to characterize RSV variants of the L-gene and other regions of the RSV genome if warranted, and to evaluate emergence of any resistance-associated mutations. Additionally, exploratory biomarkers may be assessed to determine the effects of ALS-008176 on markers of RSV disease.

An unblinded IDMC will be commissioned for this study and a Sponsor Committee will be established, refer to Section 11.12 for details. For Part 1, the IDMC will review the safety and PK data as described above. In Part 2, based on the reviews of PK, efficacy, and safety data, changes to enrollment in the treatment arms, dose regimen adjustments, or an increase in dose duration to up to 10 days may be implemented. In Part 2, a maximum of 2 formal interim

analyses are planned to assess the primary endpoint for early superiority and futility (see Section 11.11).

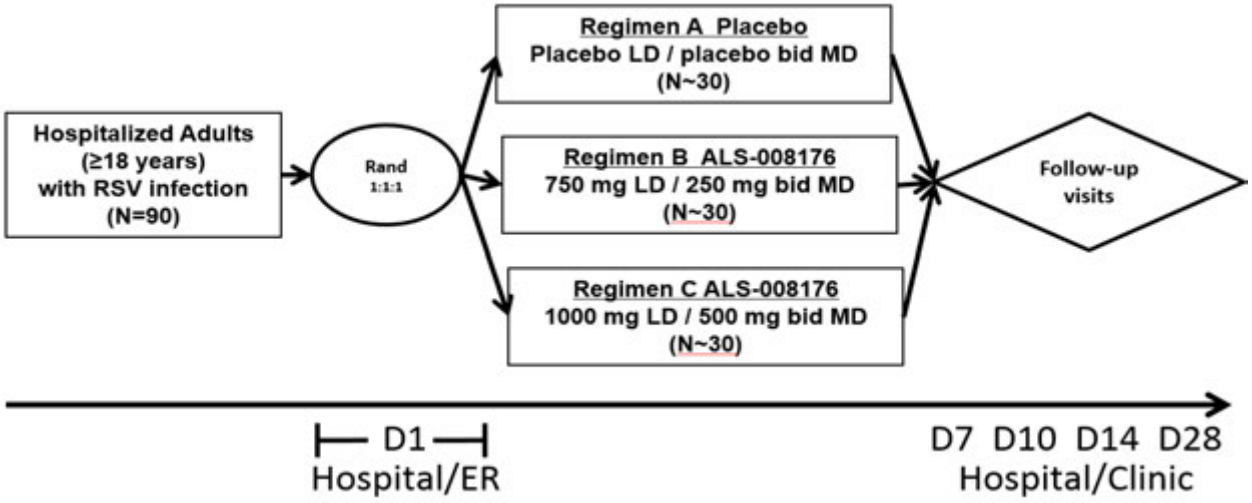
Diagrams of the study design for Part 1 and Part 2 are provided in Figure 1 and Figure 2, respectively.

Figure 1: Schematic Overview of Part 1 of the Study



Abbreviations: bid: twice daily; ER: emergency room; LD: loading dose; MD: maintenance dose; Rand: randomization

Figure 2: Schematic Overview of Part 2 of the Study



Abbreviations: bid: twice daily; ER: emergency room; LD: loading dose; MD: maintenance dose; Rand: randomization.

3.2. Study Design Rationale

Blinding, Control, Stratification, and Treatment Regimens

There is no approved treatment routinely used for the treatment of RSV infection. A placebo control will be used for both parts of the study to establish the frequency and magnitude of

changes in virologic and clinical endpoints that may occur in the absence of active treatment. The use of a placebo control will allow for any AEs or laboratory abnormalities observed during the course of the study to be evaluated properly, ie, to be able to differentiate between events potentially related to the use of ALS-008176 versus those related to the underlying disease.

Randomization will be used to minimize bias in the assignment of subjects to treatment regimens, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment regimens, and to enhance the validity of statistical comparisons across treatment regimens. In Part 1, subjects will be randomized in a 1:2 ratio to receive placebo or the low-dose ALS-008176 dosing regimen. In Part 2, subjects will be randomized in a 1:1:1 ratio to receive 1 of the ALS-008176 regimens or matching placebo. For Part 1, randomization will be stratified by region (Japan versus non-Japan). For Part 2, randomization will be stratified by region (Japan versus non-Japan) and age (≥18 to <65 years and ≥65 years). Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The number of subjects exposed as part of the study has been limited to the absolute minimum to reach the objectives of the study. For Part 2, the IDMC will be empowered such that if early superiority on the primary endpoint is established, the randomization ratio to placebo may be altered, thereby avoiding unnecessary risk and discomfort to placebo-treated subjects.

Doses Selected

The doses selected for this study are based on PK/PD modeling, which was developed to characterize the in vivo antiviral activity of ALS-008176, based on the data from the RSV challenge study in healthy volunteers (Study ALS-8176-502). The model was used to characterize the exposure-response relationships of ALS-008112. To characterize the exposure-response relationships, a semimechanistic model was utilized to describe the conversion of plasma ALS-008112 to the active NTP in lung tissue. The model was fit simultaneously to the PK and viral kinetic data for both placebo- and ALS-008176-receiving subjects from Study ALS-8176-502. A sigmoid maximum efficacy relationship described the NTP inhibition of RSV production. The model estimated the NTP 50% effective concentration and 90% effective concentration to be 1.79 μM and 2.64 μM, respectively, which is generally consistent with the reported in vitro half maximal inhibitory concentration (0.23 μM) and 90% inhibitory concentration (3 μM) against a different strain of RSV. The proposed dose regimens are projected to rapidly (within 1 to 2 hours following dosing) achieve and maintain lung tissue concentrations at least 3 times the 90% effective concentration throughout the duration of treatment in the majority of the subjects.

Because RSV is an acute infection, achieving therapeutic concentrations rapidly is an important consideration for treatment. Therefore, LD regimens were evaluated, considering not only achievement of the above targets, but also time to achieve these targets. To account for popPK variability, the probability of target attainment across the population was also considered. The assessment of twice daily dose regimens in the study is supported by the long in vitro

intracellular $t_{1/2}$ of the NTP (17.6 hours in normal human bronchial epithelial cells) and the observed sustained levels of the NTP in monkey lungs (estimated $t_{1/2}$ of approximately 29 hours).

Overall, based on the data available at the time of initial protocol writing, it is anticipated that the proposed doses are expected to be in the therapeutic range to optimize antiviral activity of ALS-008176 in adult subjects, which includes a single 750 mg LD followed by a MD regimen of 250 mg twice daily or a single 1,000 mg LD followed by an MD regimen of 500 mg twice daily. At the proposed high dose of 1,000 mg LD/500 mg MD, plasma ALS-008112 exposures in adults are projected to be at or slightly above levels observed in healthy volunteers in the RSV challenge study where potent antiviral activity against RSV was noted (AUC_{0-24h} approximately 10,000 ng.h/mL, ALS-8176-502). At the 750 mg LD/250 mg MD regimen, the projected average ALS-008112 plasma exposure is expected to be slightly more than 2-fold lower than the high dose at Day 5, which will aid in dose-response evaluation.

Simulations of the typical lung NTP exposure showed that both dose regimens rapidly achieved concentrations above EC_{90} (the highest concentration required to achieve 90% inhibition of virus replication across all RSV strains tested in vitro). Based on simulations, both a LD of 750 mg and a LD of 1,000 mg are expected to rapidly achieve the target of 3 x EC_{90}.

In Table 5, the simulations of the projected plasma exposures for the 2 regimens are shown. The simulations are based upon the popPK model that was updated with additional data of Part 1 of Study 64041575RSV2003.

Table 5: Projected Plasma Exposures of ALS-008112 at the Proposed Dose Regimens

Dose (mg)		Average Plasma AUC_{0-24h} ALS-008112 (ng.h/mL)		Average Plasma C_{max} ALS-008112 (ng/mL)	
LD	**MD**	**Day 1**	**Day 5**	**Day 1**	**Day 5**
750	250	9,273	6,854	1,555	657
1,000	500	13,215	12,100	2,027	1,221

Abbreviations: AUC_{0-24h}: area under the curve from time 0 to 24 hours after dosing; C_{max}: maximum plasma concentration.

Based on data derived from the primary analysis of Part 1 of the study, the doses to be used in Part 2 were confirmed to remain as planned.

Given the active nature of the ongoing development program, the IDMC may recommend that one of the dose regimens be removed or one or both of the dose regimens be adjusted based on safety and/or antiviral activity considerations from ongoing studies. Irrespective of the dose, the average projected ALS-008112 plasma exposure (Table 5) will not exceed a projected average AUC_{0-24h} of 20,000 ng.h/mL, a limit that is 2.5-fold lower than the lowest systemic NOAEL observed in nonclinical toxicity studies.

Treatment Duration

Treatment will last for 5 days as this was the duration of treatment assessed in healthy adult subjects infected with RSV in a human challenge model (Study ALS-8176-502), which demonstrated substantial declines in RSV RNA viral load and improvement in RSV signs and symptoms. The long terminal $t_{1/2}$ of the NTP is anticipated to provide therapeutic levels of the

active NTP beyond the 5-day dose duration. The treatment duration may be extended to up to 10 days if recommended by the IDMC, based on emerging data from the present and other ongoing clinical studies with ALS-008176.

Clinical Outcomes of RSV Treatment

Treatment with ALS-008176 may reduce the severity and duration of RSV signs and symptoms and their impact on functioning, reduce the need for and duration of supportive care (eg, oxygen supplementation, IV fluids, days of hospitalization) and accelerate the subjects' return to pre-RSV health status and HRQoL. The study will compare treatment regimens to evaluate the impact of treatment with ALS-008176 on the clinical course of RSV disease.

Biomarker Collection

Blood samples will be collected for exploratory biomarker analyses (host RNA), on the premise that these markers may play a role in the treatment response, PK, safety of ALS-008176, or the status and change of the RSV-related disease. In addition, leftover mid-turbinate nasal swabs or blood samples collected for other testing may be used for biomarker analysis (eg, proteins including cytokines) if available on the same premise. They may help to explain interindividual variability in clinical outcomes or to identify population subgroups that respond differently to the drug.

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

Biomarker analyses may be performed upon the discretion of the sponsor and will be reported separately from this study.

Medical Resource Utilization and Health Economics Data Collection

Treatment with ALS-008176 may result in lower utilization of hospital or outpatient healthcare services; therefore comparison will be done across treatment regimens.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed as soon as possible following admission to the emergency room or hospitalization, such that subjects are randomized within 5 days of RSV symptom onset. Men or women ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) diagnosed with RSV infection based on a PCR-based diagnostic assay (with or without co-infection with another respiratory pathogen) who have been (or will be) admitted to the hospital and who have signed informed consent will be enrolled. Subjects who were admitted to the hospital for another cause but develop an acute respiratory illness while being hospitalized are also eligible for screening.

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

For a discussion of the statistical considerations of subject selection, refer to Section 11.2.

4.1. Inclusion Criteria

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

1. Criterion modified per Amendment 2:

   1.1. Criterion modified per Amendment 3:

   1.2 Men or women ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place), defined at the time of randomization.

2. Hospitalized (or in emergency room prior to hospitalization) at the time of randomization and unlikely to be discharged for the first 24 hours after randomization.

3. Criterion modified per Amendment 2:

   3.1. Diagnosed with RSV infection based on PCR-based assay with or without co-infection with another respiratory pathogen (eg, influenza, human metapneumovirus, or bacteria).

   NOTE: in cases where commercial PCR-based assays are not available at the site, the sponsor should be consulted for agreement on the assay to be used.

4. Criterion modified per Amendment 2:

   4.1. Has an acute respiratory illness with signs and symptoms consistent with a viral infection (eg, fever, cough, nasal congestion, runny nose, sore throat, myalgia, lethargy, shortness of breath, or wheezing) with onset ≤5 days from the anticipated time of randomization.

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

   - An upper or lower viral respiratory tract infection (eg, “flu-like illness”)
   - Pneumonia
   - Respiratory distress
   - Asthma exacerbation
   - Chronic obstructive pulmonary disease (COPD) exacerbation

5. Criterion modified per Amendment 2:

   5.1. With the exception of the RSV disease, medically stable on the basis of medical history, physical examination, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population and/or the RSV infection. This determination must be recorded in the subject’s source documents and initialed by the investigator.

6. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal do not pose an unacceptable risk to the subject, are not clinically significant, or are appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator. A single repeat laboratory evaluation is allowed for eligibility determination.

7. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

8. Criterion modified per Amendment 2:

   8.1. A woman must have a negative urine β-human chorionic gonadotropin at screening.

9. Criterion modified per Amendment 2:

   9.1. Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

   Before randomization, a woman must be either:

   a. Not of childbearing potential defined as:

      - Postmenopausal: a postmenopausal state is defined as >45 years and no menses for 12 consecutive months without an alternative medical cause, OR
      - Permanently sterile: permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures (without reversal operation), and bilateral oophorectomy.

   b. Of childbearing potential and, if heterosexually active,

      - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

        Examples of highly effective contraceptives include

        - User-independent methods:
          implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device; intrauterine hormone-releasing system; vasectomized partner; 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 drug. 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 subject.*)

- User-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly.

- Agrees to remain on a highly effective method throughout the study and for at least 44 days after the last dose of study drug.

Note: If the childbearing potential changes after start of the study 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.

10. Criterion modified per Amendment 2:

10.1. Contraceptive use by men should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

During the study and until the end of relevant systemic exposure, plus a minimum of 1 spermatogenesis cycle (ie, 104 days in total) after receiving the last dose of study drug, a man:

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
- Who is sexually active with a pregnant woman must use a condom
- Must agree not to donate sperm

11. Criterion modified per Amendment 2:

11.1. Female partners of men must either be surgically sterilized, postmenopausal (amenorrhea for a minimum of 1 year) or, if of childbearing potential, must agree to practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) during the study and for 104 days following the last dose of study drug.

12. Criterion modified per Amendment 2:

12.1. A woman must agree not to donate eggs (ova, oocytes) during the study and for at least 44 days after receiving the last dose of study drug.

13. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Subject must have a body weight ≥50.0 kg, at screening.

4.2. Exclusion Criteria

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

1. Subjects who are not expected to survive for more than 48 hours.

2. Subjects who have had major thoracic or abdominal surgery in the 6 weeks prior to randomization.

3. Criterion modified per Amendment 2:

   3.1. Subjects who are considered by the investigator to be immunocompromised within the past 12 months, whether due to underlying medical condition (eg, malignancy or genetic disorder) or medical therapy (eg, medications other than corticosteroids for the treatment of COPD or asthma exacerbations, chemotherapy, radiation, stem cell or solid organ transplant).

4. Subjects with a known history of human immunodeficiency virus (HIV) or chronic viral hepatitis.

5. Subjects with ALT ≥3 times the upper limit of normal (ULN) AND bilirubin ≥2×ULN (direct >35%) OR ALT ≥5×ULN at screening.

6. Criterion modified per Amendment 2:

   6.1. Subjects undergoing peritoneal dialysis, hemodialysis, or hemofiltration or with an estimated glomerular filtration rate (GFR, determined by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation[15]) of <60 mL/min/1.73m^2.

$$GFR = 141 * min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} * max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} * 0.993^{Age} * sex * race$$

Legend:

Min	minimum of Scr/κ or 1
max	maximum of Scr/κ or 1
Scr	serum creatinine measured in mg/dL
κ	0.7 for women, 0.9 for men
α	-0.329 for women, -0.411 for men
Age	measured in years
Sex	1.018 for women, 1 for men
Race	1.159 for black, 1 for white and other

NOTE: The IDMC may recommend to lower the exclusionary GFR limit to <30 or <15 mL/min/1.73m^2 if any available emerging PK data in subjects with GFR ≥60 mL/min/1.73m^2 suggest that ALS-008112 exposure in the setting of moderate (ie, GFR ≥30 to <60 mL/min/1.73m^2) or severe (ie, GFR ≥15 to <30 mL/min/1.73m^2) renal impairment are projected to remain within an

acceptable range.

In the event a local site is unable to perform a CKD-EPI determination, an alternative methodology for determining GFR is permissible if discussed with and approved by the sponsor.

7. Known allergies, hypersensitivity, or intolerance to ALS-008176 or its excipients (refer to the IB).[16]

8. Criterion deleted per Amendment 2

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

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

11. Women who are pregnant or breastfeeding.

12. Criterion modified per Amendment 2:

    12.1. Men who plan to father a child while enrolled in this study or within 104 days after the last dose of study drug.

13. Subjects taking any disallowed therapies as noted in Section 8 before the planned first dose of study drug.

14. Criterion modified per Amendment 2:

    14.1. Subjects who received prescription medications intended to prevent or treat the RSV infection itself (eg, ribavirin, IV immunoglobulin, palivizumab), an investigational drug, an investigational vaccine, or used an invasive investigational medical device within 30 days or 5 half-lives (whichever is longer) before the planned first dose of study drug or is currently enrolled in an investigational study.

15. Subjects with any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

16. Subjects who have used systemic corticosteroids for >7 consecutive days immediately prior to randomization at doses higher than 20 mg/day of prednisone or equivalent.

17. Subject is being treated with extracorporeal membrane oxygenation.

18. Subjects with 1 or more of the following laboratory abnormalities at screening as defined by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (see Attachment 1):

    – Hemoglobin <9.5 g/dL

- Platelet count <75,000/mm^3
- White blood cell count <1,000/mm^3
- Absolute neutrophil count <1,000/mm^3

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once without asking prior approval from the sponsor. Retesting will be performed once within the screening window. Subjects with a normal value at retest may be included.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2 describes options for retesting. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

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

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

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

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented for both parts of this study. Subjects will be randomly assigned based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. For Part 1, randomization will be stratified by region (Japan versus non-Japan). For Part 2, randomization will be stratified by region (Japan versus non-Japan) and age (≥18 to <65 years and ≥65 years).

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

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

Under normal circumstances, the blind should not be broken until the unblinded IDMC review (see Section 11.12). The blind will also be broken for the interim analyses (see Section 11.11) or when all subjects have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. Discontinuation of study treatment should be done only for the reasons stated in Section 10.2; unblinding of study treatment should not necessarily lead to study drug discontinuation.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

6. DOSAGE AND ADMINISTRATION

The study drug ALS-008176 will be provided as tablets for oral administration. Study drug administration should start as soon as possible, but no later than 4 hours after randomization in

order to maximize the opportunity for the compound to inhibit viral replication and potentially improve outcomes.

Subjects will be dosed with a single LD followed by 9 MDs twice daily (at least 8 hours apart and maximum 16 hours apart, with no more than 2 doses per calendar day) during Day 1 to Day 5/6 (depending on the timing of the LD administration). In Part 1, subjects will be randomized in a 1:2 ratio to Regimen A or B. In Part 2, subjects will be randomized in a 1:1:1 ratio to Regimen A, B, or C.

	Regimen A[a]	**Regimen B**[a]	**Regimen C**[a]
Treatment Regimen	Placebo	Low-dose ALS-008176: 750 mg LD/250 mg MD	High-dose ALS-008176: 1,000 mg LD/500 mg MD
Loading Dose	Placebo: 1 intake of 3 tablets	ALS-008176: 1 intake of 3 x 250 mg tablet	ALS-008176: 1 intake of 2 x 500 mg tablet Placebo: 1 intake of 1 tablet
Maintenance Dose	Placebo: 9 intakes of 1 tablet	ALS-008176: 9 intakes of 1 x 250 mg tablet	ALS-008176: 9 intakes of 1 x 500 mg tablet

[a] Placebo tablets will be visually identical to their active drug counterparts.

Administration of each dose should occur at approximately the same time each day. ALS-008176 can be administered without regard to food intake. The date and time of dose administration, the date and time of food intake (limited to the food ingested within 30 minutes before or after study drug administration), and the type of food will be recorded in the eCRF during hospitalization.

In case the subject is discharged prior to the completion of dosing, study drug administration will be continued at home until all doses are administered (Day 5/6), and the date and time of dose administration will be recorded in the electronic device used for eCOA. The investigator/study-site personnel will instruct subjects on how to store the study drug for at-home use as indicated for this protocol.

An overdose in this study is defined as a calculated dose exceeding the planned dose.

7. TREATMENT COMPLIANCE

Study drug will be administered enterally.

In case a dose is missed, the dose may be given up to 6 hours after the scheduled time. If more time has elapsed the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dose schedule.

The investigator/study-site personnel will maintain a log of all study drug administered. Drug supplies for each subject will be inventoried and accounted for.

In the event of the subject being discharged (after Day 2 procedures) from hospital during the dose period, the subject will administer study drug at home and will be required to document the dose of study drug in a study medication log on the electronic device provided during screening.

The subject will receive instructions on compliance with study drug administration at the screening visit. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject who is not able to ensure compliance with the study drug.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 7 days before first dose of study drug must be recorded at screening.

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

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to the Day 28 visit (±2 days). During hospitalization, concomitant medication will be recorded by the site staff in the eCRF. Upon discharge, subjects will be required to document use of concomitant medication in the electronic device in a medication log, which will serve as basis for recording the concomitant medication in the eCRF by the site staff.

Concomitant therapies should also be recorded beyond Day 28 in the subject's medical notes and reported by SAE forms (if applicable) only in conjunction with SAEs that meet the criteria outlined in Section 12.3.2.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements, home oxygen therapy; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug/therapy, treatment phase, the dose regimen, route of administration, and its indication. Modification of an effective preexisting chronic therapy should not be made for the explicit purpose of entering a subject into the study, however if a subject has received acute doses of a prohibited drug, switching to an alternative drug chosen at the discretion of the investigator is allowed.

Concomitant medications are permitted as indicated for the management of study subjects with the exception of the medications noted here. The following medications are not permitted during the study and for the time period prior to randomization as noted:

- Moderate/strong inhibitors of OAT3: diclofenac, diflunisal, gemfibrozil, mycophenolic acid, piperacillin, probenecid, and teriflunomide (all within 24 hours prior to randomization until 24 hours after the last dose of ALS-008176).
- P-gp inhibitors and inducers such as, but not limited to: amprenavir, carbamazepine, clotrimazole, dexamethasone, fexofenadine, indinavir, morphine, nelfinavir, phenothiazine, retinoic acid, rifampin, ritonavir, saquinavir, and St John's wort (all within 24 hours prior to randomization (14 days for inducers) until 24 hours after the last dose of ALS-008176).

- Systemic medications (either chronically [more than 14 days] or within 21 days prior to randomization), which are known to modulate the host's immune response or increase viral shedding, such as immunomodulatory therapies, except for systemic corticosteroids as noted below.
- Systemic corticosteroids if used for >7 consecutive days immediately prior to randomization at doses higher than 20 mg/day of prednisone or equivalent. Subjects meeting the eligibility criteria at screening but requiring increased doses of systemic corticosteroids (>20 mg/day of prednisone or equivalent) for a prolonged period (>7 consecutive days) during the study are allowed to continue participating in the study.
- Prescription medications intended to prevent or treat the RSV infection itself (eg, ribavirin, IV immunoglobulin, palivizumab), an investigational drug, an investigational vaccine, or an invasive investigational medical device within 30 days or 5 half-lives (whichever is longer) before the planned first dose of study drug. Prescription medications intended to treat the symptoms/sequelae of the RSV infection are permitted.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, medical resource utilization, health economic, biomarker, and safety measurements applicable to this study.

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

The eCOA will be provided to the subject at screening to record the subject's ratings of the severity of the symptoms (RI-PRO), additional questions about health and functioning, and HRQoL (EQ-5D-5L) (see Attachment 2, Attachment 3, and Attachment 4, respectively). The subjects will complete the eCOA once daily throughout the study from screening to Day 28 at approximately the same time each day. The assessment on Day 1 needs to be recorded predose, before the LD. If the screening assessment was performed less than 8 hours prior to the LD, the predose assessment does not need to be performed.

The investigator/study-site personnel will provide sufficient information (included in the study manual) to enable the subject to complete the eCOA and will ensure that the eCOA is completed correctly and on schedule to avoid missing or incorrect data. If the subject is unable to complete the assessment on the device, the subject's spouse, partner, relative, friend or the investigator/study-site personnel trained on the eCOA device can read the questions and responses aloud to the subject and enter the subject's responses in the eCOA device on the subject's behalf using the interview administration procedures explained in the eCOA completion guide. If the subject is too ill at the time the eCOA is scheduled to be administered to

respond to the questions, the subject's spouse, partner, relative, friend, or the investigator/trained study-site personnel should indicate the reason the eCOA was not completed on the eCOA device for that assessment. The investigator/study-site personnel will instruct the subject to complete the eCOA questionnaires and transmit the eCOA data at approximately the same time each day from screening through end of follow-up.

Prior to completing the screening assessment, the subject (or the subject's spouse, partner, relative, or friend on the subject's behalf) must complete a training module (included as part of the eCOA device) on how to enter the subject's responses to questions in the eCOA device. If in the investigator's opinion, the subject (or the subject's spouse, partner, relative, or friend) is unlikely to reliably enter the information in the eCOA device on a daily basis for the duration of the study, the site will retain the eCOA device upon the subject's discharge and arrange for the investigator or trained study-site personnel to interview the subject by phone and record the subject's responses in the eCOA device on the subject's behalf each day post discharge to end of follow-up.

The Katz ADL questionnaire (see Attachment 5) will be completed by the investigator/study-site personnel after interviewing the subject and the data will be entered into the eCRF by the investigator/study-site personnel. The Katz ADL questionnaire will be completed twice at screening to document retrospectively the subject's pre-RSV infection functional status (ie, prior to first signs/symptoms of RSV) and the subject's current functional status (ie, after the occurrence of RSV signs/symptoms). The Katz ADL questionnaire will be completed once daily for the entire duration of hospitalization and on Day 7, Day 10, Day 14, and Day 28 if the subject is discharged.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: noninvasive procedures should be collected first before invasive procedures (eCOA completion/Katz ADL questionnaire/ECG first, then vital signs/SpO_2, then mid-turbinate nasal swab, with blood draw last). However, mid-turbinate nasal swabs for RSV RNA viral load and blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

If treatment duration is extended to up to 10 days, subjects will have an additional clinic visit 1 day (+2 days) after their last dose.

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

The maximum amount of blood drawn from each subject in this study will not exceed 110 mL.

9.1.2. Screening Phase

The procedures specified in the Time and Events Schedule will only be performed after written informed consent has been obtained. Screening may be conducted in part via a sponsor- and

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-pre-approved non-study specific screening consent process, but only if these pre-screening procedures are identical to the per protocol screening tests and are within the 48 hours window prior to screening completion. However, no study specific procedures, other than screening assessments, will be performed until the subject has signed the study-specific ICF. The non-study specific ICF will be considered source data.

Screening should be completed as soon as possible and the subject will be randomized within 5 days of RSV symptom onset to ensure the eligibility of the subject. Procedures that are standard of care and performed within approximately 48 hours prior to randomization may be used in determining study eligibility or determining baseline values. The results of the safety laboratory tests performed at the local laboratory must be in accordance with Section 4. The investigator may consider the subject eligible if the previously abnormal laboratory test result is within normal range on a repeat testing in the local laboratory. Repeat testing is only allowed once.

During screening 1 mid-turbinate nasal swab (if non-intubated) or 1 endotracheal sample (if intubated) will be collected and aliquoted for:

- RSV diagnosis using a PCR-based assay (at the local laboratory).
- RSV diagnosis confirmation using a PCR-based assay (at the central laboratory).
- Examination of viral and bacterial co-infection using multiplex PCR (at the central laboratory).
- Leftover mid-turbinate nasal swabs will be stored and may be used for biomarker research if warranted. Details on the purpose of the biomarker research are described in Section 9.5.

9.1.3. Double-blind Treatment Phase

Assessments to be performed during the treatment phase are specified in the Time and Events Schedule.

Day 1/Day of Randomization

Eligible subjects will be randomized on Day 1. Study drug administration should start as soon as possible, but no later than 4 hours after randomization. Subjects will be dosed with a single oral LD on Day 1. Depending on the time of screening/enrollment, subjects will receive the first MD of study drug on Day 1. Subjects will receive no more than 2 doses per calendar day.

Assessments to be performed on Day 1 are specified in the Time and Events Schedule. The local nasal swab sample can be used as the screening sample for the study if it fulfills the sample requirements for nasal swabs collected for study assessments. If the local sample or screening sample was taken less than 8 hours prior to the administration of the LD, the predose sample assessment (Day 1 swab) does not need to be performed. The mid-turbinate nasal swab (if non-intubated) or the mid-turbinate nasal swab and endotracheal sample (if intubated) should be taken as close as possible to and before the LD on Day 1. The timing of the LD will determine the timing of the nasal swab and endotracheal sample (if intubated). If the LD is in the morning,

all samples will be taken before the morning dose; if LD is in the afternoon, all samples will be taken before the afternoon doses but after the morning dose (Figure 3).

Figure 3: Two Scenarios for the Timing of Collection of Nasal Swabs and Endotracheal Samples (if Intubated)

Green dots represent study drug administration.
Red stars represent collection of nasal swab, and of endotracheal sample, if intubated.

Day 2 to Day 5/6 (End of Treatment)

Study drug administration continues until 10 doses have been taken. Subjects will receive 9 MDs without regard to food intake twice daily (at least 8 hours apart and maximum 16 hours apart, with no more than 2 doses per calendar day) through Day 5/6 (depending on the timing of the LD administration). The date and time of dose administration, the date and time of food intake (limited to the food ingested within 30 minutes before or after study drug administration), and the type of food will be recorded in the eCRF during hospitalization. The subject may be discharged after Day 2 following completion of study procedures. Subjects may also remain hospitalized if warranted by the subject's clinical status. In case the subject is discharged prior to the completion of treatment, study drug will continue to be administered at home by the subject until all doses are administered (Day 5/6), and the date and time of dose administration will be recorded in the electronic device used for eCOA. Instructions will be given to the subject regarding drug administration by the investigator or a qualified member of the study-site personnel.

Assessments will be performed as detailed in the Time and Events Schedule. The eCOA (investigator and subject questionnaires) and the mid-turbinate nasal swabs (if non-intubated) (from the same nostril throughout the study) or the mid-turbinate nasal swab and endotracheal samples (if intubated) are to be taken once daily prior to study drug administration at approximately the same time each day (see (Figure 3). In case of nostril bleeding or irritation during the collection of a mid-turbinate nasal swab, all subsequent nasal swabs will be performed on the contralateral nostril. Samples will be collected through Day 6 whether the subject is in hospital or has been discharged. Should the study drug duration be increased to up to 10 days (following review of the data by the IDMC), samples will be taken every day up to and including 1 day (+2 days) following the last dose of study drug. In case mid-turbinate nasal swabs are

collected at home, the subject (or the subject's spouse, partner, relative, or friend) should collect swab specimens after being trained by the investigator/study-site personnel. Subjects will be required to document the actual dates and times of collection of the nasal swab at home on the electronic device used for eCOA. Nasal swabs collected at home should be stored immediately between 2°C and 8°C (in the refrigerator) and brought to the site at the next visit.

Hospitalization duration will not be extended solely for study purposes. Telephone calls to the subjects to facilitate compliance with study procedures between outpatient study visits are permitted.

9.1.4. Posttreatment Phase (Follow-up)

Days 7 to 28

Subjects will be evaluated for a total of 28 days after randomization. If they are not hospitalized they will be required to return to the hospital for follow-up assessments as an outpatient on Day 7, Day 10, Day 14, and Day 28 as indicated in the Time and Events Schedule. On Day 28 all subjects will complete the study either as an inpatient or outpatient.

Should the study drug duration be increased to up to 10 days (following review of the data by the IDMC, refer to Section 11.12), additional study drug may be provided, if needed.

If a subject is discontinued from study drug, a follow-up visit will be scheduled 2 days (+2 days), 5 days (+2 days), 9 days (+2 days), and 23 days (±2 days) after the last dose of study drug was administered. Assessments should be performed as indicated in the Time and Events Schedule, respectively for the Day 7, Day 10, Day 14, and Day 28 visits.

9.2. Efficacy Evaluations

Viral Load Determination

As an evaluation of antiviral activity of ALS-008176, RSV RNA viral load will be measured in mid-turbinate nasal swabs (obtained from non-intubated subjects) or in mid-turbinate nasal swabs and endotracheal samples (obtained from intubated subjects or via suction through tracheostomy or other sampling methods) using qRT-PCR performed at the central laboratory. Samples for the determination of RSV viral load will be taken as specified in the Time and Events Schedule and Section 9.1.3.

RSV infectious viral load may be measured in mid-turbinate nasal swabs (if non-intubated) or in mid-turbinate nasal swabs and endotracheal samples (if intubated) using a quantitative culture method (plaque assay) in a selected number of subjects and samples at the sponsor's discretion.

Changes in viral load will be evaluated but will not be regarded as AEs or SAEs.

Viral L-gene Sequencing for Viral Resistance

Viral sequencing analysis will be performed by sequencing the polymerase L-gene and other regions of the RSV genome (may be performed if no mutations are seen in the L-gene) in samples taken before treatment (at baseline), during treatment, and posttreatment, to identify preexisting sequence polymorphisms and to characterize emerging RSV variants.

The L-gene will be sequenced pretreatment in all subjects and postbaseline in subjects not achieving viral suppression. The sequencing of postbaseline samples may be triggered at the discretion of the sponsor's virologist, based on the changes in RSV RNA viral load observed in each individual subject and the limits of the sequencing assay. The impact of newly identified mutations on in vitro antiviral activity of ALS-008176 or other RSV molecules may be assessed in in vitro studies.

Other regions of the RSV genome may also be sequenced at the sponsor's discretion.

Changes in the viral sequence will be evaluated but will not be regarded as AEs or SAEs.

Clinical Course of RSV Infection

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

- Clinical evaluation including, but not limited to:
  - Oxygen requirement type (eg, supplemental oxygen, noninvasive positive pressure ventilation, endotracheal-mechanical ventilation, mechanical ventilation by tracheostomy), duration, and amount.
  - Body weight.
  - Respiratory rate, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body temperature (method should be noted in the eCRF).
  - SpO_2.
  - Level of hospital care (eg, ICU, transitional care unit, ward floor).
  - Duration of hospitalization.
  - Need for hydration, and feeding by IV catheter/nasogastric tube.
  - Functional status (Katz ADL score).

Subject Evaluation

- Evaluation of RSV disease-related signs and symptoms and additional questions about health and functioning.
- HRQoL (EQ-5D-5L).

9.3. Pharmacokinetics

Plasma samples will be used to evaluate the PK of ALS-008112 and ALS-008144 (and other metabolites, if applicable). Samples collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. DNA analyses will not be performed on these samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Plasma samples for PK analysis will be collected at the scheduled times via an indwelling catheter and/or direct venipuncture. Saline or heparin flushes may be used to maintain viability

of indwelling catheters. The exact time of sample collection will be noted on the source document and the data collection tool.

Additional PK samples may also be collected on an ad hoc basis as a safety assessment in the event that a safety event arises for which an understanding of drug exposure is clinically important, at the discretion of the investigator or at the request of the sponsor.

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

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ALS-008112 and ALS-008144 (and other metabolites, if applicable) using a validated, specific, and sensitive liquid chromatography/mass spectrometry method by or under the supervision of the sponsor.

To maintain the study blind during the study, results of the individual PK analyses will not be shared with the investigator or sponsor representatives directly involved in managing the study.

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of ALS-008112 will be derived using popPK modeling. The estimated model parameters and individual post hoc exposure parameters (AUC, C_{min}, C_{max}) will be provided for each subject as appropriate. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant.

Intensive PK sampling in Part 1 of this study will be used to update and confirm the popPK model that was developed based on the data from healthy volunteers. Based on the PK data from hospitalized adult subjects infected with RSV from Part 1 of this study, the PK sampling for Part 2 was optimized. The popPK model may be further modified or adapted as needed.

Exposure estimates (AUC_{24h}, C_{0h}, C_{max}) will be obtained by empirical Bayesian feedback using the popPK model for ALS-008112 to assess the appropriateness of the PK and the selected doses, throughout the conduct of the study. Plasma concentration data versus time after dose of each individual will be plotted. A previously developed popPK model based on adult data from several studies will be used to overlay with the raw data. If the data fall outside the prediction interval of the model, the model will be updated. Furthermore, potential covariates (not present in the previously developed model) will be investigated graphically and can be included into the popPK model based on a significant decrease in objective function using the likelihood ratio test for nested models.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between the PK and PD (antiviral activity, clinical outcomes, and selected safety parameters) after single and repeated oral administration of ALS-008176 will be evaluated.

9.5. Biomarkers

Blood samples will be collected for exploratory biomarker analyses (host RNA), on the premise that these markers may play a role in the treatment response, PK, safety of ALS-008176, or the status and change of the RSV-related disease. In addition, leftover mid-turbinate nasal swabs or blood samples collected for other testing may be used for biomarker analysis (eg, proteins including cytokines) if available on the same premise.

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

No human DNA analyses will take place on these samples.

9.6. Medical Resource Utilization and Health Economics

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

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient).
- Duration of hospitalization (total days length of stay, including duration by wards [eg, ICU]).
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).
- Need for, and duration of, nursing home or health services from baseline to Day 28.

9.7. Safety Evaluations

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

An IDMC will be established for this study to monitor the safety of subjects. Details regarding the IDMC are provided in Section 11.12.

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

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

Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and other safety evaluations at specified time points as described in the Time and Events Schedule.

In the event that an invasive procedure such as a blood draw, mid-turbinate nasal swab, vital signs assessments, and/or ECG are required at the same time, the order of completion should be ECG first, then vital signs/SpO_2, then mid-turbinate nasal swab, then blood draw, with the mid-turbinate nasal swab and blood draw being obtained as close to the scheduled time as possible.

Adverse Events

Adverse events will be reported by the subject or the subject's legally acceptable representative for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected and analyzed by a local laboratory. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by a local laboratory as initiation of treatment is time-critical:

Hematology Panel

-hemoglobin
-hematocrit
-mean corpuscular hemoglobin
-mean corpuscular hemoglobin concentration
-platelet count
-red cell distribution width
-reticulocytes
-RBC count
-white blood cell (WBC) count

Percentage and absolute counts of:
-basophils
-eosinophils
-lymphocytes
-monocytes
-neutrophils

Serum Chemistry Panel

-alkaline phosphatase
-ALT
-AST
-bicarbonate (optional)
-blood urea nitrogen
-chloride
-creatinine
-creatine kinase
-glucose
-potassium
-sodium
-total (direct and indirect) bilirubin

Urinalysis

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

Dipstick will be performed as per the Time and Events Schedule. If dipstick is abnormal, microscopic evaluation should be performed, with evaluation of sediment as listed above.

In the microscopic examination, observations other than the presence of WBCs, RBCs, and casts may also be reported by the laboratory and need to be captured in the eCRF.

Other:

- Calculation of estimated GFR (CKD-EPI equation).
- Urine pregnancy testing for all female subjects.

Sites should attempt to collect all safety labs as defined in this protocol. In some instances, individual laboratory assessments are not routinely run at a local site. If it is not practical to obtain the results for a particular assessment due to local considerations, the sponsor study responsible physician or delegate may on a case by case basis permit individual sites to not collect that assessment.

Electrocardiogram

In Part 1 of the study, triplicate 12-lead ECGs (three 10-s recordings at approximately 60-s intervals) will be collected and analyzed by a central laboratory at screening, on Day 1, on Day 7, on Day 28, and when clinically indicated. On Day 1, triplicate ECGs will be collected at 2 time points: approximately 30 to 60 minutes and 3 to 6 hours after the LD. If an ECG is abnormal at Day 7, an additional ECG should be performed at Day 14.

In Part 2 of the study, a single 12-lead ECG will be collected and analyzed by a central laboratory at screening, on Day 4 (for subjects who remain hospitalized at this time), on Day 28, and when clinically indicated. If discharged earlier than Day 4, the subject needs to have an ECG recorded on the day of discharge. The ECG will be performed 30 minutes to 3 hours after the first dose of study drug of that day.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. 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, SpO_2, mid-turbinate nasal swabs, blood draw.

Electrocardiograms may be repeated at the investigator's discretion to account for erroneous readings.

Clinically relevant abnormalities (as defined in Attachment 6) occurring during the study should be recorded by the investigator in the AE section of the eCRF.

Vital Signs

Temperature, heart rate, respiratory rate, SBP, and DBP (methods to be noted in the eCRF) are to be collected at the time points specified in the Time and Events Schedule.

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a sitting or supine position and in a quiet setting without distractions (eg, television, cell phones). They should not be performed immediately following the administration of beta-mimetics or any supportive drug, which could affect the measurement.

Clinically relevant abnormalities (as defined in Attachment 6) occurring during the study should be recorded by the investigator in the AE section of the eCRF.

Physical Examination

A complete physical examination (including all body systems, height [only at screening], and body weight measurement) or a directed physical examination including respiratory system, nose, ear, throat, facial and neck lymph nodes, and skin examination will be performed at the visits indicated in the Time and Events Schedule.

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

The investigator must review the physical examination results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

9.7.1. Specific Toxicities

Subjects reporting skin changes or subjects with laboratory parameter changes should be followed until resolution of the toxicity and necessary standard management should be undertaken.

Skin Changes

In case there are skin changes, a correct diagnosis has to be made by the investigator or a dermatologist, preferably within 24 hours of detection. An assessment of severity grade should be made using the criteria specified in the draft DMID adult toxicity tables (see Attachment 1). Rashes should be managed as indicated in Attachment 7.

Laboratory Parameter Changes

If one (or more) of the following changes occur, the subject should discontinue study drug and should be followed until resolution (return to baseline) or stabilization of change (to be agreed upon with the sponsor). The sponsor should be informed even if the change occurs outside of the treatment period (but before the end of the study). Refer to Section 10.2 for study drug discontinuation criteria.

- Liver enzymes
  - ALT ≥3 times the ULN AND bilirubin ≥2×ULN (direct >35%) OR ALT ≥5×ULN
- Hematologic parameters
  - Hemoglobin <8.0 g/dL
  - Platelet count <50,000/mm^3
  - Absolute neutrophil count <750/mm^3

9.8. Other Evaluations

Mid-turbinate nasal swabs (if non-intubated) or endotracheal samples (if intubated) will be used to determine the presence of viral and bacterial co-infections (both by multiplex PCR) at screening.

Spirometry and DLCO tests will only be performed if the test is available at the study site and the clinical condition of the subject allows testing as judged by the investigator.

9.9. Benefit-risk Evaluations

9.9.1. Known Benefits

ALS-008176 demonstrated a significant antiviral effect and reduced the signs and symptoms of RSV infection in the RSV human challenge model. However, the clinical benefit of this compound in the treatment of RSV infection remains to be fully established.

9.9.2. Potential Benefits

Subjects participating in this study might have a benefit regarding the clinical course of their RSV infection. Results from ALS-008176 clinical studies may be useful in developing a new therapy for RSV infection.

9.9.3. Known Risks

All therapies have the potential to cause adverse experiences.

A formal adverse drug reaction analysis has not yet been conducted for ALS-008176, known risks associated with ALS-008176 have not been identified.

9.9.4. Potential Risks

The nonclinical toxicity profile for ALS-008112 was similar to that previously observed for other marketed nucleoside analogs, where hematopoietic changes and genotoxicity were noted.

The toxicity profile established for ALS-008112 in nonclinical toxicology studies indicates a reversible and dose-related effect on the hematopoietic system where changes in bone marrow cytology were associated with changes in hematological parameters. Specifically, decreased circulating reticulocytes, changes in RBC-related parameters, and hypocellularity of erythroid cell lines in the bone marrow were observed, next to changes on white blood cells, mostly lymphocytes and neutrophils, along with changes in the bone marrow myeloid cells and lymphoid organs. Thrombocytopenia was seen in the dog at very high exposure.

As of 02 January 2018, in adult subjects hospitalized with RSV, 2 hematological serious/severe AEs have occurred and subsequently resolved. In these 2 cases (pancytopenia SAE in Study 64041575RSV2003; severe neutropenia in Study ALS-8176-510), the subject received ALS-008176, but both cases were confounded by multiple medical comorbidities and recent/concomitant use of multiple medications that have been reported to cause bone marrow toxicity. In addition, two Grade 4 SAEs of (febrile) neutropenia (laboratory Grade 4) considered possibly related to the study drug were reported in hospitalized pediatric subjects infected with RSV (1 subject in the MAD part of Study ALS-8176-503 and 1 subject in Study 64041575RSV2004).

Based on the available information, hematopoietic toxicity is considered a potential risk for ALS-008176 for adult and pediatric subjects, for which continued close monitoring of hematological parameters and clinical status in both RSV- and hMPV-infected and healthy subjects is warranted, as additional data are being collected in ongoing/future studies with ALS-008176. Importantly, these hematological side effects observed in both nonclinical and clinical studies with ALS-008176 were reversible.

In addition, in nonclinical studies, ALS-008112 has been shown to cause clastogenicity, specifically breakage of chromosomes, through a non-DNA-reactive, indirect mechanism, resulting from an imbalance of intracellular nucleotide pools. The threshold of clastogenicity for ALS-008112, as defined by the lowest concentration where an effect was observed, from in vitro studies was 10 µg/mL and from in vivo studies was an AUC of 107,983 ng.h/mL. The NOEL for genotoxicity of ALS-008112 from in vitro studies was 5 µg/mL and for in vivo studies was an AUC of 57,595 ng.h/mL.

Considering the clastogenicity changes in animal studies, clastogenicity is considered a potential risk for ALS-008176, and therefore ALS-008112 plasma exposures for human subjects will be limited to a maximum average $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL (or 25,200 ng.h/mL in whole blood) for any given dose. With this threshold, exposures for adults and infants are respectively at least

2.5-fold and 4.7-fold lower than the lowest systemic NOAEL exposure obtained in nonclinical toxicity studies, thereby providing an adequate safety margin.

The effect of ALS-008176 on developmental and reproductive parameters in animals appears to be primarily a decrease in fetal weights in rats at high doses of 400 mg/kg twice daily and an increase in post-implantation losses in pregnant rabbits at doses of 20 mg/kg twice daily and higher, with no teratogenic effects in fetuses in either rats or rabbits. In addition, there were no adverse effects on fertility endpoints in male rats up to the highest dose tested of 250 mg/kg twice daily or in female rats up to 75 mg/kg twice daily.

Potential risks associated with ALS-008176 administration that might occur in humans are based on theoretical known risks associated with other nucleoside analogs. Theoretical risks for nucleoside analogs are neuropathy, mitochondrial dysfunction, myopathy (including cardiomyopathy), lactic acidosis, hepatomegaly with steatosis, and pancreatitis. None of these theoretical risks have been observed in ALS-008176 studies to date.

All antivirals carry the potential risk of inducing drug resistance. However, it is not expected that the clinical course of the subject will be substantially influenced by the emergence of resistance, as RSV infection is a self-limiting disease and the subject's immune system will be able to eventually clear the virus.

Heterosexually active women must be of non-childbearing potential, defined as being postmenopausal or permanently sterile (see Section 4.1), or can be of childbearing potential when practicing a highly effective method of contraception, and must agree not to donate eggs (ova, oocytes) during the study and for at least 44 days after receiving the last dose of study drug.

During the study and until the end of relevant systemic exposure, plus a minimum of 1 spermatogenesis cycle (ie, 104 days in total) after receiving the last dose of study drug, a man who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception. A man who is sexually active with a pregnant woman must use a condom, and must not donate sperm.

9.9.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this study is acceptable for the following reasons:

- Careful study of the safety, PK, and preliminary efficacy of ALS-008176 as an antiviral treatment for RSV is the first step in addressing an unmet medical need.
- No safety concerns have previously been raised based on the safety information from healthy adult subjects and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to ALS-008176 by the investigator.
- Safety concerns have been raised based on safety information from hospitalized adult subjects infected with RSV. To reduce risk to subjects, the design of the study has been adapted to explore the PK, safety, and tolerability of the low-dose ALS-008176 dosing

regimen before proceeding with Part 2 of the study including a high-dose ALS-008176 dosing regimen.

- To reduce risk to subjects, ALS-008112 plasma exposures for human subjects will be limited to a maximum average $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL (or 25,200 ng.h/mL in whole blood) for any given dose. This threshold provides safety margins that are at least 2.5-fold and 4.7-fold lower for adults and infants, respectively, than the lowest systemic NOAEL exposure obtained in nonclinical toxicity studies.
- Several safety measures have been implemented to minimize potential risk and stress to subjects, including:
  - Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
  - Utilization of discontinuation and withdrawal criteria (see Section 10.2).
  - Subjects are to be hospitalized upon treatment initiation allowing for intensive monitoring.
  - Close monitoring of subjects throughout the study (see Section 17.9).
  - Safety surveillance in this study will monitor standard safety parameters associated with investigational drug development, known possible risks of ALS-008176 exposure and theoretical risks attributed to the nucleoside drug class.
  - Utilization of data obtained from standard of care samples.
  - The establishment of an IDMC to monitor data on a regular basis to ensure continuing safety of the subjects enrolled in this study.

9.10. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF. 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. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent) or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Refer to Attachment 8 for details on PK sampling.

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

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

10.1. Completion

A subject will be considered to have completed the treatment phase of the study if he or she has completed the treatment regimen and the Day 7 visit or the visit 1 day (+2 days) after the final dose of study drug if the study drug administration is increased to up to 10 days following IDMC review of the data. A subject will be considered to have completed the study if he or she has completed assessments of the last follow-up visit.

10.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment

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

A subject's study treatment must be discontinued if:

- The subject withdraws consent.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.
- The subject has an eGFR ≤30 mL/min/1.73 m² according to the CKD-EPI equation.
- The subject experiences any of the laboratory abnormalities as specified in Section 9.7.1.

If a subject discontinues study drug before the end of the treatment phase, the subject will be encouraged to continue with end-of-treatment and follow-up assessments in accordance with the Time and Events Schedule.

Withdrawal From the Study

Each subject has the right to withdraw at any time for whatever reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact the subjects who do not return for scheduled visits or follow-up. Although the subjects are not obliged to give reason(s) for withdrawing early, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

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

- Lost to follow-up.
- Withdrawal of consent.
- Death.
- The subject is poorly compliant with study procedures, study drug administration, visits, and assessments, after evaluation and discussion between the investigator and sponsor.

- Decision by the sponsor to stop or cancel the study.
- Decision by the investigator to withdraw subjects.
- Decision by local regulatory authorities and IEC/IRB to stop or cancel the study.

If a subject withdraws from the study before the end of the treatment phase, the subject will be encouraged to continue with end-of-treatment and follow-up assessments in accordance with the Time and Events Schedule.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the treatment phase, end-of-treatment and follow-up assessments should be obtained.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding research samples:

- The collected (scavenged) samples will be retained and used in accordance with the subject's original informed consent for research samples.
- The subject may withdraw consent for exploratory biomarker research, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact of withdrawal of consent for the research samples and to request sample destruction. The sponsor study-site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP) that will be prepared for each part of the study. The SAP for the IDMC will be separate from the SAP of the final analysis. In addition, a separate SAP for the interim analyses of Part 2 will be prepared.

The primary analysis of Part 1 will be done after a target of approximately 24 subjects have been enrolled and have completed treatment, preferably after the end of a hemispheric season. The primary unblinded analysis will be performed once the Day 14 PK, safety, and tolerability data are available, and data have been locked. Additional data obtained after database lock of this analysis will either be analyzed after Part 2 for integrated safety and efficacy purposes or may be analyzed in a separate analysis after all subjects enrolled in Part 1 have completed the study. Efficacy data of Part 1 will not be included in inferential models of dose finding for Part 2, but will be part of an integrated efficacy analysis.

All subjects enrolled into each part of the study who receive at least 1 dose of study drug will be included in the safety population. Subjects in this population will be defined by the drug actually received, not by randomization assignment. Any subject who receives a single dose of ALS-008176 will thus be included in the ALS-008176 arm and all subjects that receive only placebo will be included in the placebo arm. The safety population will be used for all safety analyses. Furthermore, an integrated analysis of the safety data will be done across both study parts using pooled data for active and placebo treatment groups. The 2 subjects who were already enrolled before the implementation of this protocol amendment will also be included in this analysis.

For each part of the study, all subjects who are randomized, have an RSV infection confirmed by central laboratory assessment, and who receive at least 1 dose of study drug will constitute the intent-to-treat (ITT) infected population. Treatment assignment for this population will be defined by randomization assignment. The ITT infected population will be used for all efficacy/virologic analyses. For the analysis of Part 2, only data from Part 2 will be used. For data from both Parts 1 and 2 also integrated analyses will be prepared, analogous to those of Part 2.

For Part 2, the per-protocol population will be defined as all subjects included in the ITT infected population without protocol deviations that affect efficacy assessment. The per-protocol population will be established during the blinded data review and may be used to perform sensitivity analysis on the primary endpoint.

11.1. Subject Information

All demographic characteristics and other initial subject characteristics will be tabulated and analyzed descriptively. Treatment adherence to ALS-008176 will be derived from the collected information.

11.2. Sample Size Determination

No formal hypothesis is specified for Part 1 of this study. Part 1 is intended to characterize the PK and to confirm the popPK model derived from healthy volunteers in hospitalized adult subjects infected with RSV. Furthermore the safety and tolerability of the low-dose ALS-008176 treatment regimen will be assessed. The number of subjects participating in Part 1 is considered sufficient to achieve the objectives of the characterization of the PK in Part 1 and allows for

updating the PK model, if deemed necessary, based on the results (potential covariates) found in Part 1.

A total sample size of 15 to 16 subjects on active treatment would provide 80% power to achieve a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and central volume of distribution, assuming a between subject variation of 50% (coefficient of variation) as based on 10,000 simulations of the current popPK model.[12] For the secondary objective of safety assessment the probability was calculated to observe an (S)AE that has a true incidence of 1% which would be 15% with a total sample size of 16 subjects on active treatment; the probability to observe an (S)AE with a true incidence of 0.1%, 0.5% and 0.8% is 2%, 8% and 12%, respectively. Therefore, the current sample size of 16 subjects on active treatment is deemed adequate for Part 1.

For Part 2, the primary hypothesis is a positive dose-response relationship for the AUC of active treatment regimens. The positive dose-response relationship assumes that dose regimens with higher exposure with respect to MD will have at least an equal or better effect on viral load. Therefore 2 contrasts will be tested at each of the interim analysis points and final analysis; a contrast with no difference between the 2 active regimens tested against placebo and a contrast with a positive linear dose-response relationship with respect to active regimens. With respect to multiple contrast testing, multiplicity will be controlled at the prespecified (interim) alpha level by calculating adjusted p-values from the simulated distribution of the maximum or maximum absolute value of a multivariate t random vector (ie, using the correlation between the contrasts to optimally control for alpha).[11] The overall (family-wise) type 1 error rate of 2.5% (1-sided) will be adjusted for multiple testing due to formal interim analyses using an O'Brien-Fleming alpha spending function with 3 sequential tests (2 interim, 1 final).[13] As based on 10,000 simulations a sample size of 90 subjects randomized in a 1:1:1 ratio (placebo: low-dose ALS-008176: high-dose ALS-008176) will offer approximately 90% power to detect a positive dose-response relationship as defined assuming an effect size of 0.77 using Cohen's d (ie, the effect size expressed as the ratio of the standard deviation of the AUC) and approximately 80% power assuming an effect size of 0.67 (Cohen's d). Based on the results of the ALS-008176 RSV human challenge study, these effect sizes were considered plausible.[9] The results of Part 1 did not lead to changes in the assumptions underlying the sample size determination.

11.3. Efficacy Analyses

Primary Endpoint

For Part 2, the primary endpoint in this study is RSV RNA $\log_{10}$ viral load (measured by qRT-PCR in the mid-turbinate nasal swab specimens) AUC immediately prior to first dose of study drug (baseline) over 7 days. Mean $\log_{10}$ viral load values over time will be analyzed using a restricted maximum likelihood based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure will be used to model the within-subject errors over time. The differences in the AUCs for active versus placebo will be derived using

appropriate contrasts deriving least square mean differences, including the 95% 2-sided confidence intervals. For inferential purposes, p-values will be compared with significance levels controlling for the (family-wise) type 1 error rate. Details will be provided in the SAP that will be finalized before the first formal interim analysis of Part 2.

Secondary Endpoints

The secondary endpoint of time to clinical stability is defined as the time at which the following criteria are all met:

- normalization of blood oxygen level (return to baseline, pulse oximetry) without requirement of supplemental oxygen beyond baseline level
- normalization of oral feeding
- normalization of respiratory rate
- normalization of heart rate

Normalization criteria will be specified in the SAP. Subjects for which no time point could be established (eg, withdrawal of informed consent before reaching the endpoint or no clinical stability at last observation) will be (right-) censored at the latest time point at which it could be established that clinical stability was not reached. The differences in time to clinical stability of active dose regimens versus placebo treatment will be estimated using a Cox proportional hazard model; as baseline covariates, stratification factors, absence/presence of other viral or bacterial infections, baseline $\log_{10}$ viral load, and time from onset of first symptoms to treatment will be added. Treatment effect versus placebo will be reported, including 95% confidence intervals. In case the proportional hazards assumption is not satisfied, appropriate sensitivity analyses will be performed as detailed in the SAP.

The ordinal scale consists of 6 categories that are exhaustive, mutually exclusive, and ordered (Table 6). For all subjects, the category at Day 5/6 (depending on the timing of the LD administration) will be established as the worst category on that day. For example, if a subject is discharged on Day 6, the category will be non-ICU and no supplemental oxygen (if there was no supplemental oxygen given on that day). The analysis will be performed using a proportional odds model, modeling the common odds ratio of the improvement on the ordinal scale of active treatment versus control. Baseline covariates that are predictive of the ordinal scale may be added to the model to increase the model fit. In case of missing data (>10%), a multiple imputation method under the missing-at-random assumption will be employed. Details will be provided in the SAP.

Table 6: Ordinal Scale on Day 5/6 (Depending on the Timing of the LD Administration)

Outcome
Death
Admitted to ICU
Non-ICU hospitalization requiring supplemental oxygen
Non-ICU hospitalization not requiring supplemental oxygen
Not hospitalized, unable to resume normal activities
Not hospitalized, resumption of normal activities

ICU = Intensive Care Unit

A secondary endpoint of high interest is the length of hospital stay. The length of hospital stay is in hours and taken from the start of treatment initiation to discharge and to readiness for discharge. The differences of active dose regimens versus placebo treatment will be estimated using the accelerated failure time model using appropriate contrasts; baseline covariates such as stratification factors, absence/presence of other viral or bacterial pathogens, RSV baseline $\log_{10}$ viral load, and time from onset of first symptoms to treatment will be added when of predictive value based on blinded data. Treatment effects versus placebo will be reported as acceleration factors including 95% confidence intervals. Subjects for which no time point could be established (eg, withdrawal of informed consent before reaching the endpoint) will be (right-)censored at the latest time point at which it could be established that the endpoint was not reached. Subjects for whom discharge cannot be considered as a marker of adequate recovery (eg, subjects who die during hospitalization or who are transferred to a care facility with the same level of care as during hospitalization) will be censored at the planned final follow-up visit. No adjustments for multiplicity will be made. Analytical details will be provided in the SAP.

While this clinical endpoint is considered of high interest, the current sample size is determined by considerations on antiviral activity; for length of hospital stay the anticipation is that there will be too much heterogeneity to expect statistically significant separation of active groups versus placebo with the current sample size, even if a numerical trend is anticipated.

The impact of the baseline viral genotype and subtype on the antiviral activity will be explored.

Analysis of the viral sequencing results will be described in the SAP.

11.4. Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of ALS-008112 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (eg, demographics, laboratory variables, race) will be tested as potential covariates affecting PK parameters. Details will be given in a popPK analysis plan and the key findings of the popPK analysis will be presented in the final clinical study report.

A snapshot date for PK samples to be analyzed for the planned primary analysis for Part 1 and interim analyses for Part 2 will be defined. Samples collected before this snapshot date will be analyzed for ALS-008112 and ALS-008144 and included in the popPK analysis (for ALS-008112 only). Samples collected after the snapshot date will be analyzed at a later date, and

will be included in a popPK re-analysis when they become available after interim analysis database lock.

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

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

For each treatment group, descriptive statistics, including arithmetic mean, standard deviation, CV, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of ALS-008112 and ALS-008144, if applicable.

11.5. Biomarker Analysis

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

11.6. Pharmacokinetic/Pharmacodynamic Analyses

Efficacy and safety parameters will be subject to PK/PD analysis at the end of each part of the study. ALS-008112 exposures will be evaluated as an independent variable, with selected efficacy and selected safety parameters considered as dependent variables. Various approaches, including graphical analysis, linear, nonlinear, and logistic regression methods may be utilized.

The key findings of the PK/PD analysis will be presented in the final clinical study report.

11.7. Subject Clinical Outcome Assessments

Subject-reported eCOA (RI-PRO, additional questions about health and functioning, and HRQoL [EQ-5D-5L]) data will be descriptively summarized by treatment group and compared across treatment groups.

11.8. Katz Activities of Daily Living

The investigator-reported Katz ADL data will be descriptively summarized by treatment group and compared across treatment groups.

11.9. Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics will be descriptively summarized by treatment group and compared across treatment groups.

11.10. Safety Analyses

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

Adverse Events

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

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. 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 posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The laboratory abnormalities will be determined according to the criteria specified in the draft Division of Microbiology and Infectious Diseases Adult Toxicity Table (see Attachment 1) and in accordance with the normal ranges of the clinical laboratory if no gradings are available.

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 at each scheduled time point (the predose ECG will be used as baseline). Frequency tabulations of the abnormalities will be made.

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 method: QT corrected according to Fridericia's formula (QTcF). The percentage of subjects with abnormalities as defined in Attachment 6 will be tabulated.

Vital Signs

Descriptive statistics of temperature, heart rate, respiratory rate, SBP, and DBP values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits (as defined in Attachment 6) will be summarized.

Physical Examination

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.11. Interim Analysis

For Part 2, a maximum of 2 formal interim analyses are planned to assess the primary endpoint for early superiority and futility. The first formal interim analysis will be performed when at least 45 subjects have completed treatment to ensure that adequate data is available for interim analysis review, preferably after the end of a hemispheric RSV season. Up to the final database lock, the study team will remain blinded to the results. Details on operational characteristics will be provided in the interim analysis charter.

The following situations will be considered based on the results of the analysis of the primary endpoint at this stage: that the study is considered futile; that superiority can be concluded (based on an O'Brien-Fleming alpha spending function); that the study is considered underpowered; or that the study should continue unchanged. In the case of the (unbinding) futility boundary being crossed, the IDMC will recommend early termination to the Sponsor Committee. If the study is considered underpowered, a sample size increase may be suggested to a maximum of 180 subjects. This blinded sample size calculation will take the residual error variance into account of the primary analysis model.

If early superiority on the primary endpoint can be established, the study may, however, be continued in order to accumulate data to allow the selection of the dose regimen or further substantiate the benefit-risk profile in this population; in this case the randomization ratio of active to placebo treatment may be altered for example, if dose selection is evident from the dose-response analysis, subjects randomized to active treatment may all receive the optimal dose. However, at the interim analyses or at any time, upon recommendation by the IDMC, a dose regimen may be removed or adjusted based on PK, safety, and/or antiviral activity considerations.

The Interim Analysis Committee will be responsible for performing the formal interim analysis and will consist of sponsor personnel who are not otherwise involved in the study. The IDMC will review the data and make recommendations to the Sponsor Committee.

11.12. Independent Data Monitoring Committee

An IDMC will be established to monitor data in both parts of the study and will review data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in

this study and to evaluate whether efficacy objectives are met. A Sponsor Committee will also be established and will be responsible for identifying appropriate actions based on the recommendations of the IDMC as described in the IDMC charter.

The IDMC will meet periodically to review interim data. After the review, the IDMC will make recommendations to the Sponsor Committee regarding the continuation of the study. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician, 1 of whom will chair the committee. The IDMC responsibilities, authorities, and procedures will be documented in its charter. Other members may be required dependent on the nature of the interim analysis (refer to Section 11.11).

For Part 1, the IDMC will review the safety and PK data after approximately 12 subjects have completed treatment as per the IDMC charter. When approximately 24 subjects have completed the Day 14 follow-up visit, an unblinded primary analysis will be performed by the sponsor for review by the IDMC. For Part 2, the IDMC will review the safety data initially after approximately 12 subjects have completed treatment and when approximately 12 Japanese subjects have completed treatment to assess that treatment may safely continue in each arm and will continue to assess PK, efficacy, and safety during the conduct of the study. Enrollment will continue while the IDMC reviews the data unless otherwise instructed by the IDMC. The frequency of IDMC reviews will be detailed in the IDMC charter.

Given the challenges of ensuring study site preparation in time to recruit for an acute seasonal infection like RSV and the delays caused by implementing an amendment during an RSV season, the doses, treatment regimen, and/or duration of dosing of ALS-008176 may be modified by recommendation of the IDMC at any time for PK, efficacy, or safety reasons based on the review of this study and other ongoing studies of ALS-008176. The duration of dosing, if extended, will not exceed 10 days and the doses will not exceed those resulting in an expected average ALS-008112 plasma $AUC_{0\text{-}24h}$ of 20,000 ng.h/mL (or 25,200 ng.h/mL in whole blood), a limit that is 2.5-fold lower than the lowest systemic NOAEL exposure observed in nonclinical toxicity studies. If the IDMC determines that subjects with a duration of RSV symptoms of 5 days prior to randomization may not achieve benefit based on interim results, the allowed duration of the time of onset of RSV symptoms to the time of randomization may be reduced. In addition, if the IDMC determines that subjects with a duration of RSV symptoms longer than 5 days prior to randomization may achieve benefit based on interim results, this duration may be increased to up to 7 days (ie, 7 days from symptom onset to randomization). If such modifications are recommended by the IDMC and endorsed by the sponsor, these changes will be communicated in writing to investigators, health authorities, and IECs/IRBs and may be implemented without amendment to this protocol.

In Part 2, based on the reviews of PK, efficacy, and safety data by the IDMC, changes to enrollment in the treatment arms, dose regimen adjustments, sample size adjustments, or an increase in dose duration to up to 10 days may be implemented.

Sponsor personnel involved in this process will not be involved in the conduct of the study. Details are provided in the IDMC charter.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1 for time of last AE recording).

Serious Adverse Event

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

- Results in death.
- Is life-threatening.
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is medically important*.

  *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ALS-008176, expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

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

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

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

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

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All AE and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related

procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

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

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

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

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

12.3.2. Serious Adverse Events

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

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

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

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

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

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

  Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

If the subject is re-hospitalized after discharge for the same RSV disease, this will constitute an SAE.

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

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

Because the study drug may have an effect on sperm, pregnancies in partners of men 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.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The ALS-008176 and matching placebo supplied for this study is formulated as white to off-white film-coated tablets. The active tablets contain 250 mg or 500 mg ALS-008176 and have the same appearance of tablet size, shape, and color. Placebo tablets are visually identical to their active drug counterparts. It will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

14.2. Packaging

The tablets are packaged in round white high-density polyethylene bottles, with an induction seal and a white polypropylene child-resistant closure.

All study drugs will be supplied to the site in blinded containers.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All study drug should be stored at controlled room temperature.

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

14.5. Drug Accountability

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- ALS-008176 IB and any addenda.
- Pharmacy manual/study-site investigational product and procedures manual.
- Laboratory manual.
- Electronic device for investigator and subject eCOA.

- Completion guide(s) for eCOA.
- PCR machine for RSV diagnosis (if needed).
- Specimen collection kits for blood (PK and biomarker host RNA) and mid-turbinate nasal swab.
- Contact information page(s).
- IWRS manual.
- eCRF completion guidelines.

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

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

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

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

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

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

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

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

16.2.3. Informed Consent

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

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

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

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

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

16.2.4. Privacy of Personal Data

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

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

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

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ALS-008176, to understand RSV, to understand differential drug responders, and to develop tests/assays related to ALS-008176 and RSV disease. The research may begin at any time during the study or the poststudy storage period. No human DNA testing will be performed.

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

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

The doses or treatment regimen of ALS-008176 may be modified by recommendation of the IDMC at any time for PK, efficacy, or safety reasons based on the review of this and other ongoing studies of ALS-008176. If such modifications are recommended based on IDMC review, these changes will be communicated in writing to investigators, health authorities, and IECs/IRBs and may be implemented without amendment to this protocol.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification

and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

17.4. Source Documentation

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

Additionally; patient-reported outcomes (data for the eCOA will be captured directly in the electronic instrument, which will serve as source documentation) and the Katz ADL score (the questionnaire will be completed by the investigator after interviewing the subject and the data will be entered into the eCRF by the investigator/study-site personnel) will be considered source data.

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 may be considered source data:

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

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

- Discharge summaries.

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

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

17.5. Case Report Form Completion

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

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

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

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

If necessary, queries will be generated in the electronic data capture 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 electronic data capture tool at their own initiative or as a response to an auto query (generated by the electronic data capture tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.5.1. Katz Activities of Daily Living

The investigator will provide information about the subject's health status, symptoms, and behavior after interviewing the subject at time points noted in the Time and Events Schedule. The Katz ADL questionnaire (see Attachment 5) will be completed by the investigator after interviewing the subject and the data will be entered into the eCRF by the investigator/study-site personnel.

17.6. Subject Clinical Outcome Assessments

Clinical Outcome Assessments (RI-PRO, additional questions about health and functioning, and HRQoL [EQ-5D-5L], see Attachment 2, Attachment 3, and Attachment 4, respectively) will be completed on an electronic device provided at the study site. Responses provided will be recorded directly in the electronic database. Site coordinators should monitor the site management website, provided by the eVendor, on a daily basis to ensure information is uploaded from these devices as required.

Each day from screening though end of follow-up, the investigator/study-site personnel will monitor whether the subject's eCOA data were uploaded to the eCOA website provided for this study. If more than 36 hours have elapsed since the last eCOA assessment was recorded on the eCOA website, the investigator/study-site personnel will contact the subject (or the subject's spouse, partner, relative, or friend) to ensure that the eCOA questionnaires are completed and transmitted to the server every day, to identify problems collecting or transmitting the assessments, and to instruct the subject/person entering the subject's responses on the eCOA device on the way to correct any problems with collecting or transmitting the eCOA data. Telephone calls to the subjects to facilitate compliance with the study procedures between outpatient study visits are permitted.

Study monitors should monitor completion of the eCOA and follow-up with sites immediately should there be any indication that the eCOA is not being completed or if data transfer is not being done as scheduled.

The eCOA device includes built-in training for study-site personnel, investigators, and subjects.

The subject will provide information about his/her health status, symptoms, functional status, and HRQoL on an electronic device at time points noted in the Time and Events Schedule. In addition, after hospital discharge, the subject will record study drug and concomitant medications administered on the electronic device in a medication log. All subject assessments and logs will be provided in the native language of the subject. The electronic device will include instructions and training that will be completed upon first use by the subject (or the subject's spouse, partner, relative, or friend) and will be available on demand thereafter if the subject chooses this option. If the subject is unable to complete the assessments on the eCOA device, the subject's spouse, partner, relative, friend or the investigator/study-site personnel who has completed the training on use of the eCOA device can read the questions and response options aloud to the subject and enter the subject's responses in the eCOA device on the subject's behalf using the interview administration procedures explained in the eCOA completion guide. In case the subject and his/her delegate experience problems with entering the data in the electronic device after discharge of the subject from the hospital, the investigator or trained study-site personnel can provide data entry support by phone. During hospitalization, if the subject is unable to complete the assessment on the device and the subject's spouse, partner, relative, or friend is not available to enter the subject's responses on the device for the subject, the investigator or trained study-site personnel can read the questions and response options to the subject and record the subject's responses on the device on the subject's behalf. If in the investigator's opinion, the subject (or

the subject's spouse, partner, relative, or friend) is unlikely to reliably enter the information in the eCOA device on a daily basis for the duration of the study, the site will retain the eCOA device upon the subject's discharge and arrange for the investigator or trained study-site personnel to interview the subject by phone and record the subject's responses in the eCOA device on the subject's behalf each day post discharge to end of follow-up.

17.7. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory 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 the investigator/study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.8. Record Retention

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

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

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

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

17.9. Monitoring

The sponsor will use a combination of monitoring techniques as specified in the monitoring guidelines, 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 postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and the investigator/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 investigator/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 investigator/study-site personnel. The sponsor expects that, during monitoring visits, the investigator and/or 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, the investigator/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.

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

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

17.10.2. Study Termination

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

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

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

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

17.11. On-site Audits

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

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

17.12. Use of Information and Publication

All information, including but not limited to information regarding ALS-008176 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ALS-008176, 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 subject

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

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

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Toxicity Tables

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) ADULT TOXICITY TABLE – NOVEMBER 2007 (DRAFT)

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-THREATENINGAEs

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/d L	8.0 - 9.4gm/dL	6.5 - 7.9 gm/d L	< 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/d L 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/d L 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/d L	11.6 - 12.5 mg/d L	12.6 - 13.5 mg/d L	> 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/d L	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 red blood cell casts	obstructive or required transfusion

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

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

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

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

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

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

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

Attachment 2: Respiratory Infection Symptom Questionnaire©

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

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

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

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

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

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

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

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

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

Attachment 3: Additional Questions About Health and Functioning

Adult RSV Additional Questions[a]

For each of the following questions please select one response only

1. Did you take any medicine for your respiratory infection symptoms today?

   - ☐ Yes
   - ☐ No

2. Did you use any rescue medicine today for asthma or COPD?

   - ☐ I do not take medicine for asthma or COPD
   - ☐ Yes
   - ☐ No

3. Since this time yesterday, how much of the time did you breathe oxygen from an oxygen tank?

   - ☐ None of the time
   - ☐ Less than an hour
   - ☐ 1 to 4 hours
   - ☐ More than 4 hours

4. Overall, how severe were your respiratory infection symptoms today?

   - ☐ No respiratory infection symptoms today
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very Severe

5. Overall, how were your respiratory infection symptoms today compared to yesterday?

   - ☐ Much better
   - ☐ Somewhat better
   - ☐ A little better
   - ☐ About the same
   - ☐ A little worse
   - ☐ Somewhat worse
   - ☐ Much worse

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

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

7. Have you returned to your usual activities today?

- ☐ Yes
- ☐ No

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

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

9. Have you returned to your usual health today?

- ☐ Yes
- ☐ No

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

Questions 1-3 are only completed during outpatient follow-up as this information will be collected in the eCRF during hospitalization.

Attachment 4: EuroQol 5-Dimension Questionnaire (EQ-5D)

Health Questionnaire

English version for the USA

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

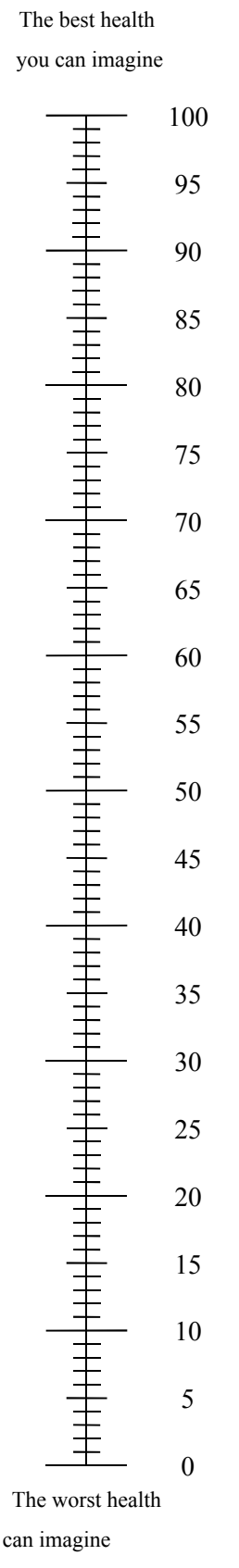
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Attachment 5: Katz Activities of Daily Living

Katz index of independence in activities of daily living

Activities	Independence	Dependence
Points (1 or 0)	**Points (1)** ***NO*** **supervision, direction, or personal assistance**	**Points (0)** ***WITH*** **supervision, direction, personal assistance or total care**
Bathing POINTS:_____	**(1 point)** Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	**(0 points)** Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
Dressing POINTS:_____	**(1 point)** Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	**(0 points)** Needs help with dressing self or needs to be completely dressed.
Toileting POINTS:_____	**(1 point)** Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	**(0 points)** Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
Transferring POINTS:_____	**(1 point)** Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	**(0 points)** Needs help in moving from bed to chair or requires a complete transfer.
Continence POINTS:_____	**(1 point)** Exercises complete self control over urination and defecation.	**(0 points)** Is partially or totally incontinent of bowel or bladder.
Feeding POINTS:_____	**(1 point)** Gets food from plate into mouth without help. Preparation of food may be done by another person.	**(0 points)** Needs partial or total help with feeding or requires parenteral feeding.
Total points:_____		

6 points: high (patient independent).

0 points: low (patient very dependent).

Attachment 6: Cardiovascular Safety - Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	HR	**PR**	**QRS**	**$QT_{corrected}$**
Abnormalities on actual values				
Abnormally low	< 45 bpm	< 110 ms	-	-
Abnormally high	≥ 120 bpm	> 220 ms	≥ 120 ms	-
Borderline prolonged QT (males)	-	-	-	450 ms < QTc ≤ 480 ms
Borderline prolonged QT (females)	-	-	-	470 ms < QTc ≤ 480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤ 500 ms
Pathologically prolonged QT	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc < 30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤ 60 ms
Abnormally high QTc change	-	-	-	ΔQTc > 60 ms

For absolute QTc parameters the categories are defined based on the ICH E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

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

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.

[b] The classification of AEs related to hypotension and hypertension will be done according to the WHO grading scale.

Attachment 7: Visit Schedule for Rash Management for Adult Subjects

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

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 1 of rash[1]	• Study medication may be continued. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (preferably within 24h). • Referral to dermatologist (preferably within 24h) **ONLY IF** rash diagnosis or relationship with study medication is uncertain.	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (preferably within 24h). • Referral to dermatologist (preferably within 24h) **ONLY IF** rash diagnosis or relationship with study medication is uncertain.	• Study medication **MUST** be permanently **DISCONTINUED**. Rechallenge is **NOT ALLOWED**. • Unscheduled visit for initial rash evaluation **REQUIRED**. • Digital pictures **REQUIRED** (within 24h). • Referral to dermatologist **REQUIRED** (preferably within 24h). • At discretion of the investigator or at request of the dermatologist, assessment of safety blood sample. • Biopsy **ONLY IF** required by dermatologist.
Day 2	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED**.	• Follow-up visit **REQUIRED**.[2] • Digital pictures **REQUIRED**.	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**.
Day 3	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 4	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 5	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**. • Digital pictures **REQUIRED**. • At discretion of the investigator or at request of the dermatologist, assessment of safety blood sample.
Day 6	No rash follow-up visit required.[2]	No rash follow-up visit required.[2]	• Follow-up visit **REQUIRED**.

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

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

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

Attachment 8: Details for Pharmacokinetic Sampling and Collection of Food Intake Information

These tables summarize the details on PK sampling and collection of food intake information.

Part 1

Dose #	Dose Name	Day	PK Sample[a]	Food Intake Information Collected (Yes/No)?[a,b]
1	LD	1	3 samples postdose at 0.5-1h, 2-3h, and 4-6h	Yes[c]
2	MD 1	1 or 2	3 samples predose, and postdose at 0.5-1.5h and 3-6h	Yes[c]
3	MD 2	2	1 sample if patient has not been discharged: predose (preferable), or random sample	Yes[c]
4	MD 3	2 or 3	No	No
5	MD 4	3	No	No
6	MD 5	3 or 4	No	No
7	MD 6	4	No	No
8	MD 7	4 or 5	No	No
9	MD 8	5	No	No
10	MD 9	5 or 6	1 sample	Yes[c]
NA	NA	7	1 sample (random sample at visit)	No
NA	NA	10	1 sample (random sample at visit)	No

Part 2

Dose #	Dose Name	Day	PK Sample[a]	Food Intake Information Collected (Yes/No)?[a,b]
1	LD	1	2 samples postdose at 0.5-1h and 2-3h	Yes[c]
2	MD 1	1 or 2	2 samples predose, and postdose at 3-6h	Yes[c]
3	MD 2	2	1 sample if patient has not been discharged: predose (preferable), or random sample	Yes[c]
4	MD 3	2 or 3	No	No
5	MD 4	3	No	No
6	MD 5	3 or 4	No	No
7	MD 6	4	No	No
8	MD 7	4 or 5	No	No
9	MD 8	5	No	No
10	MD 9	5 or 6	1 sample if patient has not been discharged: predose (preferable), or random sample	Yes[c]
NA	NA	7	1 sample (random sample at visit)	No
NA	NA	10	1 sample (random sample at visit)	No

Abbreviations: LD: loading dose; MD: maintenance dose; NA: not applicable, PK: pharmacokinetic(s).

[a] At the day of discharge, if subject is receiving study drug, a random PK sample is required and also food intake needs to be recorded.

[b] Record the food intake 30 minutes before or after study drug administration.

[c] For hospitalized subjects only.

INVESTIGATOR AGREEMENT

I have read this document 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 document and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Guy De La Rosa

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the document Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
Guy De la rosa	20Mar2018, 12:15:21 PM, UTC	Document Approval