Janssen Research & Development*

Clinical Protocol

A Long-term Follow-up of Study 64041575RSV2004 to Evaluate the Impact of Lumicitabine (JNJ-64041575) on the Incidence of Asthma and/or Wheezing in Infants and Children with a History of Respiratory Syncytial Virus Infection

Protocol 64041575RSV2002; Phase 2b
AMENDMENT 2

Lumicitabine (JNJ-64041575, ALS-008176)

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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: 2016-002095-26

Status: Approved
Date: 30 January 2018
Prepared by: Janssen Research & Development, a Division of Janssen Pharmaceutica NV.
EDMS number: EDMS-ERI-116070484, 6.0

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

Protocol History 64041575RSV2002		
Document Type and *File Name*	Issued Date	Comments
Initial Clinical Protocol *64041575RSV2002_Protocol*	14 June 2016	-
Protocol Amendment 1 *64041575RSV2002_Protocol_Amend_1*	26 June 2017	For details, please refer to Amendment 1
Protocol Amendment 2 *64041575RSV2002_Protocol_Amend_2*	This document.	For details, please refer to Amendment 2

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PROTOCOL AMENDMENTS

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (This document)

This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for this amendment was to provide more clarity when the clinician questionnaire needs to be completed. Furthermore, it was clarified that the entry visit needs to take place within 3 months after randomization in Study 64041575RSV2004 and that the study site visits need to be scheduled 3, 6, 12, 18, and 24 months after entry visit in Study 64041575RSV2002.

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

Rationale: It was clarified that the clinician questionnaire needs to be completed during the scheduled study site visits (entry visit and 3, 6, 12, 18, and 24 months after entry visit) and during monthly telephone calls with the parent/caregiver between study site visits as indicated in the Time and Events Schedule. Instructions in the paper questionnaire and footnote "b" of the Time and Events Schedule were updated accordingly. Furthermore, it was clarified that the entry visit needs to take place within 3 months after randomization in Study 64041575RSV2004 and that the study site visits need to be scheduled 3, 6, 12, 18, and 24 months after entry visit in Study 64041575RSV2002.

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Rationale: A window of ±7 days from the entry visit is allowed for the other scheduled study site visits.

Time and Events Schedule

Rationale: The protocol is aligned with the sponsor's latest available protocol template and minor corrections were made, including but not limited to:

- The classification of this study as an observational or interventional study depends on local regulation. Therefore the word "observational" was removed from the protocol.

Throughout the protocol

Amendment 1 (26 June 2017)

This amendment is considered to be nonsubstantial 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, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for this amendment was to clarify that participation in this long-term follow-up study is optional for study sites, update the study number for which this study will be the long-term follow-up study (64014575RSV2004), update the introduction and background information to be in line with Study 64014575RSV2004, update the age of subjects participating in Study 64014575RSV2004, and update the planned number of subjects to be enrolled in Study 64041575RSV2004. 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: Language was added to clarify that participation in this long-term follow-up study is optional for study sites.

SYNOPSIS
3.1 Overview of Study Design

Rationale: The study number for Study 64041575RSV2001 was changed to 64041575RSV2004. Due to significant changes in the study design a new protocol number was created for this study. Additional changes were also made to align Study 64041575RSV2002 with Study 64041575RSV2004 and included the following:

- The introduction and background information was updated to be in line with Study 64041575RSV2004 and the updated version of the Investigator's Brochure (Edition 7).
- The age of infants and children participating in Study 64041575RSV2004 was updated from 1 to 36 months to ≥28 days to ≤36 months, according to the 64041575RSV2004 protocol.
- The planned number of subjects to be enrolled in Study 64041575RSV2004 was updated according to the 64041575RSV2004 protocol.

Throughout the protocol
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Rationale: Minor editorial changes, clarifications, and corrections were made, including but not limited to:

- The generic name of the investigational product, lumicitabine, was added. The compound numbers of the investigational product and its metabolites were also updated to the current compound numbers.
- A definition was added to explain that "previous treatment group" refers to the actual treatment (lumicitabine or placebo) administered in Study 64041575RSV2004.
- Clarification was made that wheezing and medication parent/caregiver cards will be completed on a daily basis and that these cards will aid the study site personnel to complete the clinical questionnaire when they interview the parent/caregiver. The wheezing and medication parent/caregiver cards were added as attachments to the protocol.
- A paper questionnaire instead of an electronic device will be used for completion of the clinical questionnaire.

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SYNOPSIS

A Long-term Follow-up of Study 64041575RSV2004 to Evaluate the Impact of Lumicitabine (JNJ-64041575) on the Incidence of Asthma and/or Wheezing in Infants and Children with a History of Respiratory Syncytial Virus Infection

Lumicitabine (also known as JNJ-64041575 or ALS-008176) is a 3',5'-bisisobutyrate prodrug of the cytidine nucleoside analog JNJ-63549109 (also known as ALS-008112), which is being developed as an orally administered antiviral therapy for the treatment of infants, children, and adults infected with respiratory syncytial virus (RSV) and human metapneumovirus. Once administered, lumicitabine is rapidly and efficiently converted by esterases to JNJ-63549109. Inside cells, JNJ-63549109 is subsequently converted to the JNJ-63549109-5'-triphosphate, JNJ-65409136 (also known as ALS-008136), which, as the active metabolite of the compound, is a potent and selective inhibitor of RSV and human metapneumovirus ribonucleic acid (RNA) polymerase activity via a classic chain termination mechanism. JNJ-64167896 (also known as ALS-008144), the uridine metabolite of JNJ-63549109, is the inactive major metabolite noted in systemic circulation.

Investigational Product and its Metabolites

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

Abbreviation: NTP: nucleoside triphosphate.

This long-term follow-up (LTFU) study will evaluate the incidence of the clinical diagnosis of asthma and the frequency of wheezing for at least 2 years in subjects enrolled from Study 64041575RSV2004.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

The primary objectives are to evaluate in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004 during the follow-up period and within 2 years after the RSV infection:

- The incidence of the clinical diagnosis of asthma.
- The frequency of wheezing.

Secondary Objectives

The secondary objectives are to evaluate during the follow-up period in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004:

- The frequency of wheezing over time.
- The frequency of wheezing episodes over time.
- The long-term safety of lumicitabine.

- The frequency and type of respiratory infections.
- Medical resource utilization.

Exploratory Objectives

The exploratory objectives are to evaluate during the follow-up period in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004:

- The long-term impact of RSV and its treatment with lumicitabine or placebo on how the subject's health affects normal daily activities for subjects, parents/caregivers, and other family members.
- Impact of the type of wheezing/asthma phenotypes on the frequency of wheezing and clinical diagnosis of asthma.

Endpoints

Primary Endpoints

The primary endpoints are:

- Clinical diagnosis of asthma within the first 2 years after the RSV infection, as diagnosed by a physician and reported by the parent/caregiver.

  All medical information needed to confirm the diagnosis of asthma needs to be collected by the study site personnel.
- Percentage of wheezing days within the first 2 years after the RSV infection, based on information reported by the parent/caregiver.

Secondary Endpoints

The secondary endpoints during the follow-up period are:

- Percentage of wheezing days per month after the RSV infection, based on information reported by the parent/caregiver.
- Number of wheezing episodes after the RSV infection, based on information reported by the parent/caregiver.
- Incidence of reportable adverse events (AEs) and serious adverse events (SAEs) among subjects, based on information reported by the parent/caregiver and judged by the investigator. Reportable AEs include AEs related to respiratory illnesses and AEs considered at least possibly related to lumicitabine or placebo by the investigator.
- Number and type of respiratory infections among subjects, based on information reported by the parent/caregiver.
- Medical resource utilization including the number of medical visits, emergency room visits, and hospitalizations, all for respiratory conditions only, based on information reported by the parent/caregiver.

Exploratory Endpoints

The exploratory endpoints during the follow-up period are:

- The long-term impact of RSV and its treatment with lumicitabine or placebo on how the subject's health affects the normal daily activities of the subject, the parent/caregiver, and other family members as determined by:
  - The extent to which the subject's daily activities each month were limited by the subject's health.
  - The percentage of days each month that the parent/caregiver missed from work due to the subject's health.
  - The extent to which the parent's/caregiver's productivity while at work was limited by the subject's health.
  - The extent to which the subject's health problems limited the parent's/caregiver's ability to engage in normal daily activities.
  - The extent to which the subject's health problems impacted the parent's/caregiver's health.
  - The inability of the parent/caregiver to care for other family members due to the subject's health.
  - The extent to which the subject's health limited the parent's/caregiver's time spent with other family members.
  - The percentage of days each month that other family members missed from work due to the subject's health problems.
- Frequency of wheezing and clinical diagnosis of asthma by type of wheezing/asthma phenotype.

Hypothesis

No formal hypothesis testing will be performed. The hypothesis to be explored is that treatment of RSV-infected infants and children with lumicitabine will decrease the incidence of subsequent asthma and/or wheezing compared with infants and children treated with placebo.

OVERVIEW OF STUDY DESIGN

This is a global, multicenter, blinded, LTFU study to evaluate the incidence of the clinical diagnosis of asthma and the frequency of wheezing in infants and children (otherwise healthy or with underlying comorbidities for severe RSV) who have completed their treatment course and their last study-related visit in a previous Phase 2 study, 64041575RSV2004, in which they received lumicitabine or placebo for the treatment of RSV infection. Subjects will be followed for at least 2 years following treatment. This study may be extended up to an additional 3 years (ie, total duration up to 5 years after randomization into Study 64041575RSV2004). Participation in this LTFU study is optional for study sites. This LTFU study will be offered to subjects of Study 64041575RSV2004 if their site decides to participate in this LTFU study.

Subjects will be enrolled within 3 months after randomization in Study 64041575RSV2004.

No study drug will be administered in this study. The parent/caregiver of the subject and the investigator will remain blinded to the study treatment (lumicitabine or placebo) administered in Study 64041575RSV2004 until the completion of this LTFU study, including any extension period.

Assessments will be performed at the study site at enrollment in this study and at 3, 6, 12, 18, and 24 months after entry visit in Study 64041575RSV2002. The last visit of Study 64041575RSV2004 (ie,

Day 28) may be combined with the entry visit of this LTFU study. The same assessments will be performed during monthly phone calls with the parent/caregiver between the study site visits.

An unblinded interim analysis will be performed when all subjects from the first season in Study 64041575RSV2004 who are enrolled in this LTFU study complete the 18 month follow-up assessment of this LTFU study. This interim analysis will serve to evaluate the need for an extension of the follow-up period.

SUBJECT POPULATION

Male or female infants and children who were previously randomized in Study 64041575RSV2004 for the treatment of RSV infection, who completed the planned course of the study drug and the last study-related visit in Study 64041575RSV2004, and whose legally acceptable representative has signed the informed consent form are eligible for participation in this LTFU study.

DOSAGE AND ADMINISTRATION

No study drug will be administered in this study.

CLINICAL EVALUATIONS

The study includes the following clinical evaluations:

- Collection of information on the clinical diagnosis of asthma to determine the incidence of asthma.
- Collection of presence of wheezing on a daily basis to determine the frequency of wheezing and wheezing episodes.
- Collection of medical history and family history to identify risk factors for wheezing/asthma at baseline.
- Collection of data to determine the frequency and type of respiratory infections.
- Collection of data on medications used for the treatment of respiratory infections and illnesses (eg, bronchodilators).
- Collection of data from lung function tests and allergy tests (immunoglobulin E and skin test), if available, as supporting documentation of the diagnosis of asthma, wheezing, and atopy.

MEDICAL RESOURCE USAGE AND HEALTH ECONOMICS

Medical resource usage (including medical visits, emergency room visits, and hospitalizations, all for respiratory conditions) and the impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members will be collected throughout the course of the study.

SAFETY EVALUATIONS

The study includes the following evaluations of safety and tolerability:

- Respiratory illness AEs (including subsequent RSV infections).
- AEs considered at least possibly related to lumicitabine or placebo.
- SAEs.

STATISTICAL METHODS

No formal power calculation has been performed, as this is an LTFU study in which infants and children from the previous Phase 2 study of lumicitabine (Study 64041575RSV2004) may be enrolled. The planned number of subjects enrolled in Study 64041575RSV2004 is up to 120 subjects on lumicitabine

and up to 60 subjects on placebo. It is expected that approximately 35% of those subjects will participate in this LTFU study.

The final analysis will be done when all the subjects have completed the last planned assessment of the follow-up period or discontinued earlier.

The primary endpoints in this study are the clinical diagnosis of asthma and the percentage of wheezing days in a subject within the first 2 years after the RSV infection, as reported by the parent/caregiver.

No statistical testing will be done.

Estimates of the incidence of asthma will be presented together with the 95% (2-sided) confidence interval by previous treatment group. The previous treatment group is defined as the actual treatment (lumicitabine or placebo) of Study 64041575RSV2004. As a sensitivity analysis, the incidence of asthma will be presented for the subgroup of subjects for whom at least 12 months of follow-up data are available.

The percentage of days with wheezing within the first 2 years after the RSV infection will be calculated per subject. Descriptive statistics, including 95% confidence intervals, will be presented by previous treatment group.

For the secondary endpoint, descriptive statistics and frequency tabulations will be used to present the percentage of wheezing days per month, the mean number of wheezing episodes, and the number and type of respiratory infections by previous treatment group.

Long-term safety of lumicitabine, medical resource utilization, and impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members will be evaluated using frequency tabulations and listings by previous treatment group.

TIME AND EVENTS SCHEDULE

Study Period	Entry Visit[a,b]	Assessment Period[b]				
Months	0	3 (±7 days)	6 (±7 days)	12 (±7 days)	18 (±7 days)	24 (±7 days)
Screening/Administrative						
Informed consent	X					
Eligibility criteria	X					
Baseline demographics[c]	X					
Medical and family history[c,d]	X					
Wheezing and medication parent/caregiver card distribution and verification[e,f]	X	X	X	X	X	X
Clinical Evaluations						
Clinician questionnaire[g]	X	X	X	X	X	X
	Monthly telephone calls between study site visits[h]					
Collection of data from lung function tests and allergy tests (immunoglobulin E and skin tests)[i]	X					
Medical resource utilization[j]	X					
Medication[f]	X					
Safety Evaluations						
Serious/reportable adverse events[k]	X					

a. The entry visit needs to take place within 3 months after randomization in Study 64041575RSV2004. The last visit of Study 64041575RSV2004 (ie, Day 28) may be used as the entry visit for this study.
b. Assessments will be performed during study site visits (entry visit and 3, 6, 12, 18, and 24 months after entry visit in Study64041575RSV2002) and during monthly telephone calls with the parent/caregiver between study site visits.
c. Baseline demographics and medical/family history from the previous Phase 2 Study 64041575RSV2004 will be captured in the long-term follow-up electronic case report form (eCRF).
d. Medical and family history to identify risk factors for wheezing/asthma at baseline, including prenatal smoking by the subject's mother, subject's exposure to tobacco smoke, wheezing associated with symptoms of acute respiratory infections, whether the subject has siblings or attends kindergarten/day care, and personal and/or family history of atopy/allergy will be recorded in the eCRF.
e. Parents/caregivers will be provided with a wheezing parent/caregiver card to be completed daily. The information recorded on the wheezing parent/caregiver card will aid the site responsible person to complete the clinical questionnaire when interviewing the subject's parent/caregiver. Parents/caregivers will be required to return the completed parent/caregiver cards to the study sites every 3 months (eg, in person or by mail/email/fax when no study site visit is scheduled).
f. Medication use will be monitored throughout the study from signing of the informed consent form until the last study-related activity. Parents/caregivers will be required to bring all medications to the study site visit. Additionally, parents/caregivers will be required to document on a daily basis use of all medications on a medication parent/caregiver card, which will serve as a reminder card to be used during the study site visits and during the monthly phone calls between the study site visits for recording the medication used for respiratory infections and illnesses in the eCRF by the study site personnel. Parents/caregivers will be required to return the completed parent/caregiver cards to the study sites every 3 months (eg, in person or by mail/email/fax when no study site visit is scheduled).
g. Collection of data on wheezing, asthma, eczema, allergic rhinitis, and impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members using a standardized questionnaire. The questionnaire should preferably be completed by the same study site responsible person, by

interviewing the subject's parent/caregiver. Parents/caregivers will complete the wheezing and medication parent/caregiver cards on a daily basis, which will aid the study site responsible person in completing the questionnaire during the interview. Parents/caregivers will be required to return the completed parent/caregiver cards to the study sites every 3 months (eg, in person or by mail/email/fax when no study site visit is scheduled).

h. Once per calendar month (±7 days) from the entry visit.
i. Data from lung function tests and allergy tests (immunoglobulin E and skin test), if available, will be collected as supporting documentation of the diagnosis of asthma, wheezing, and atopy as reported by the parent/caregiver.
j. Medical resource utilization will be monitored throughout the study from signing of the informed consent form until the last study-related activity and will include medical visits, emergency room visits, and hospitalizations, all for respiratory conditions only and will be recorded in the eCRF. Visits with each type of health care provider (eg, general practitioner, pediatrician, physician assistant, nurse practitioner, pulmonologist, allergist, or other) will be specified in the eCRF.
k. All reportable adverse events and serious adverse events will be monitored throughout the study from signing of the informed consent form until the last study-related activity and recorded in the eCRF.

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CYP	cytochrome P450
DMID	Division of Microbiology and Infectious Diseases
eCRF	electronic case report form
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LD	loading dose
LRTI	lower respiratory tract infection
LTFU	long-term follow-up
MD	maintenance dose
NTP	nucleoside triphosphate
OAT	organic anion transporter
PK	pharmacokinetic(s)
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SAE	serious adverse event
SUSAR	serious unexpected suspected adverse reaction

1. INTRODUCTION

Respiratory syncytial virus (RSV) is a ribonucleic acid (RNA) virus and a member of the *Pneumoviridae* family, which also includes human metapneumovirus. 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.[3]

RSV causes acute lower respiratory tract infection (LRTI) and is a major cause of hospital admissions and death in young children worldwide. RSV is a leading cause of lower respiratory disease in infants.[9] In 2005, an estimated 33.8 million episodes of RSV LRTI occurred worldwide in infants. Of these, at least 3.4 million severe cases of LRTI required hospitalization, and an estimated 66,000 to 199,000 deaths occurred, mostly in the developing world.[9] In the United States, it has been estimated that annually RSV infection causes 2.1 million emergency room or outpatient visits, including 57,527 hospitalizations.[7] Infants that are born prematurely or close to the RSV season and/or suffering from bronchopulmonary dysplasia or congenital heart disease are at the highest risk of developing severe RSV-related acute LRTI.[6]

RSV infection has been strongly associated with subsequent childhood asthma and wheezing, although the relationship has not been clearly defined.[4,5] A causal relationship of RSV to subsequent development of asthma is supported by studies showing that the prophylactic use of Synagis® (palivizumab) to prevent RSV infection can decrease the subsequent incidence of recurrent wheezing in high risk infants.[2,11,12,13] In one such study, physician-diagnosed recurrent wheezing was observed in 6.4% and 18.9% of infants in the palivizumab-treated and -untreated groups, respectively ($p < 0.001$). This difference remained significant after adjustment for known risk factors of recurrent wheezing ($p < 0.001$).[13] The American Academy of Pediatrics has however questioned the validity of these findings, describing the reduction of wheezing episodes among recipients of palivizumab as being statistically significant but of clinically minimal significance.[1] A recent study in Native American infants with an efficacious anti-RSV monoclonal antibody (motavizumab), despite reducing RSV admission to hospital by 87%, did not have any impact on medically attended recurrent wheezing.[10]

Asthma appears to be a heterogeneous condition, with signs, symptoms, and clinical evolution that vary according to the patient's disease characteristics or phenotype.[4] Asthma is defined and diagnosed through a combination of clinical symptoms and physiologic abnormalities, generally without reliance upon pathologic or biologic markers. However, the physiologic definition of asthma is relatively nonspecific, consisting of airway hyperreactivity and airflow limitation during expiration, which is variable and/or reversible with bronchodilators. In many asthma patients, the presence of bronchial hyperreactivity is never objectively confirmed.

Three wheezing/asthma phenotypes have been identified: early transient wheezers, non-atopic preschool wheezers, and atopic asthmatics/wheezers. Potential risk factors for each of these classic wheezing/asthma phenotypes presenting in children include prenatal smoking by the subject's mother, subject's exposure to tobacco smoke, wheezing associated with symptoms of acute respiratory infections, whether the subject has siblings or attends kindergarten/day care, personal and/or family history of atopy/allergy, and lung function.[4]

Lumicitabine (also known as JNJ-64041575 or ALS-008176) is a 3',5'-bisisobutyrate prodrug, which is readily metabolized to the cytidine nucleoside analog, JNJ-63549109 (also known as ALS-008112). Once administered, lumicitabine is rapidly and efficiently converted by esterases to JNJ-63549109. Inside cells, JNJ-63549109 is subsequently converted to JNJ-63549109-5'-triphosphate, JNJ-65409136 (also known as ALS-008136), which, as the active metabolite of the compound, is a potent and selective inhibitor of RSV and human metapneumovirus RNA polymerase activity via a classic chain termination mechanism. JNJ-64167896 (also known as ALS-008144), the uridine metabolite of JNJ-63549109, is the inactive major metabolite detected in systemic circulation. Table 1 gives an overview of the investigational product used in this study and its metabolites, including the prior and current compound numbers.

Table 1: Investigational Product and its Metabolites

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

Abbreviation: NTP: nucleoside triphosphate.

For the most comprehensive nonclinical and clinical information regarding lumicitabine, refer to the latest version of the Investigator's Brochure (IB).[8]

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 is a long-term follow-up (LTFU) of Study 64041575RSV2004, which evaluates the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics (PK) of orally administered lumicitabine regimens in infants and children aged ≥28 days to ≤36 months hospitalized with RSV infection in Study 64041575RSV2004 whose parents/caregivers consented for participation in the LTFU study. This LTFU study, Study 64041575RSV2002, will follow these infants and children for at least 2 years after completion of their treatment course and their final visit of Study 64041575RSV2004 to evaluate the incidence of the clinical diagnosis of asthma and the frequency of wheezing.

A summary of the major findings from nonclinical and clinical studies available at the time of initial protocol writing is presented below. Please refer to the IB for more details.[8]

Nonclinical Studies

The antiviral activity and selectivity of the parent nucleoside JNJ-63549109 and its prodrug, lumicitabine, were demonstrated 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, lumicitabine was evaluated in the African Green monkey model of RSV infection.

The nonclinical safety profiles for lumicitabine and JNJ-63549109 have been established in multiple in vitro and in vivo studies. In general, lumicitabine was well tolerated in adult rats and dogs for 14 days with no mortality or overt signs of toxicity when administered orally twice daily. In juvenile toxicity studies, doses of 1,000 mg/kg/day caused overt toxicity in both rats and dogs (JNJ-63549109 area under the concentration time curve from time zero to 24 hours postdose of ≥300,000 and ≥1,375,000 ng.h/mL in rats and dogs, respectively).

In studies investigating the PK and metabolism profile, the prodrug, lumicitabine, was rapidly and efficiently converted to the parent nucleoside, JNJ-63549109, following both intravenous and oral administration in all species studied. Lumicitabine exhibited high systemic clearance and short half-life. JNJ-64167896, the uridine metabolite of JNJ-63549109, was a major metabolite noted in systemic circulation in monkeys, but not in other species.

Lumicitabine and its major metabolites are predicted to have low potential for cytochrome P450 (CYP)- and transporter-mediated drug-drug interactions, with the possible exception of strong organic anion transporter (OAT) 3 inhibitors.

Clinical Studies

The efficacy of lumicitabine in naturally infected populations has not been demonstrated; however, efficacy has been assessed in healthy adult subjects infected with RSV in a human challenge model (Study ALS-8176-502). In this study, in 62 healthy adult subjects inoculated with RSV and treated with lumicitabine or placebo, data demonstrated that maintenance doses (MDs) of 150 to 500 mg lumicitabine, following a 750 mg loading dose (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.

Data from 6 Phase 1/2a studies (ALS-8176-501, ALS-8176-502, ALS-8176-504, ALS-8176-509, 64041575RSV1001 [ALS-8176-511], and 64041575RSV1003) in healthy adult subjects (N=234), indicate that lumicitabine was well tolerated and that no safety concerns were identified after receiving lumicitabine 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 MD (twice daily, every 12 hours) for up to 13 days.

As of 20 April 2017, there have been 2 hematologic serious adverse events (SAEs) of pancytopenia and neutropenia reported in the ongoing clinical studies in hospitalized adult or pediatric subjects with RSV infection, respectively. In addition, there has been 1 non-serious Grade 4 hematologic adverse event (AE) (neutropenia, laboratory Grade 4) in the terminated Study ALS-8176-510 in an adult hospitalized subject with RSV infection. The safety data for all 3 studies have been regularly reviewed by unblinded Independent Data Monitoring Committee, which have identified no potential safety concerns. Factors other than treatment with lumicitabine, including underlying RSV infection, are more likely to have contributed to these serious/severe hematologic AEs. However, a potential contribution of lumicitabine cannot be excluded. The risk-benefit assessment for the continued development of lumicitabine remains

favorable given the population targeted (hospitalized subjects) and the lack of available treatment for RSV infection.

1.2. Overall Rationale for the Study

Given the anticipated effect of lumicitabine treatment on RSV viral kinetics and clinical symptoms (see Section 1), the potential impact on subsequent wheezing and asthma is of interest. This study will therefore evaluate the long-term impact of treatment of RSV infection with lumicitabine on the subsequent development of wheezing or asthma.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

The primary objectives are to evaluate in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004 during the follow-up period and within 2 years after the RSV infection:

- The incidence of the clinical diagnosis of asthma.
- The frequency of wheezing.

Secondary Objectives

The secondary objectives are to evaluate during the follow-up period in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004:

- The frequency of wheezing over time.
- The frequency of wheezing episodes over time.
- The long-term safety of lumicitabine.
- The frequency and type of respiratory infections.
- Medical resource utilization.

Exploratory Objectives

The exploratory objectives are to evaluate during the follow-up period in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004:

- The long-term impact of RSV and its treatment with lumicitabine or placebo on how the subject's health affects normal daily activities for subjects, parents/caregivers, and other family members.
- Impact of the type of wheezing/asthma phenotypes on the frequency of wheezing and clinical diagnosis of asthma.

2.1.2. Endpoints

Primary Endpoints

The primary endpoints are:

- Clinical diagnosis of asthma within the first 2 years after the RSV infection, as diagnosed by a physician and reported by the parent/caregiver.

  All medical information needed to confirm the diagnosis of asthma needs to be collected by the study site personnel.
- Percentage of wheezing days within the first 2 years after the RSV infection, based on information reported by the parent/caregiver.

Secondary Endpoints

The secondary endpoints during the follow-up period are:

- Percentage of wheezing days per month after the RSV infection, based on information reported by the parent/caregiver.
- Number of wheezing episodes after the RSV infection, based on information reported by the parent/caregiver.
- Incidence of reportable AEs and SAEs among subjects, based on information reported by the parent/caregiver and judged by the investigator. Reportable AEs include AEs related to respiratory illnesses and AEs considered at least possibly related to lumicitabine or placebo by the investigator.
- Number and type of respiratory infections among subjects, based on information reported by the parent/caregiver.
- Medical resource utilization including the number of medical visits, emergency room visits, and hospitalizations, all for respiratory conditions only, based on information reported by the parent/caregiver.

Exploratory Endpoints

The exploratory endpoints during the follow-up period are:

- The long-term impact of RSV and its treatment with lumicitabine or placebo on how the subject's health affects the normal daily activities of the subject, the parent/caregiver, and other family members as determined by:
  - The extent to which the subject's daily activities each month were limited by the subject's health.
  - The percentage of days each month that the parent/caregiver missed from work due to the subject's health.
  - The extent to which the parent's/caregiver's productivity while at work was limited by the subject's health.

  - The extent to which the subject's health problems limited the parent's/caregiver's ability to engage in normal daily activities.
  - The extent to which the subject's health problems impacted the parent's/caregiver's health.
  - The inability of the parent/caregiver to care for other family members due to the subject's health.
  - The extent to which the subject's health limited the parent's/caregiver's time spent with other family members.
  - The percentage of days each month that other family members missed from work due to the subject's health problems.
- Frequency of wheezing and clinical diagnosis of asthma by type of wheezing/asthma phenotype.

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

No formal hypothesis testing will be performed. The hypothesis to be explored is that treatment of RSV-infected infants and children with lumicitabine will decrease the incidence of subsequent asthma and/or wheezing compared with infants and children treated with placebo.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a global multicenter, blinded, LTFU study to evaluate the incidence of the clinical diagnosis of asthma and the frequency of wheezing in infants and children (otherwise healthy or with underlying comorbidities for severe RSV) who have completed their treatment course and their last planned study-related visit in a previous Phase 2 study, 64041575RSV2004, in which they received lumicitabine or placebo for the treatment of RSV infection. Subjects will be followed for at least 2 years following treatment. Participation in this LTFU study is optional for study sites. This LTFU study will be offered to subjects of Study 64041575RSV2004 if their site decides to participate in the LTFU.

No study drug will be administered in this study. Subjects may be enrolled within 3 months after randomization in Study 64041575RSV2004. Assessments will be performed at the time points specified in the Time and Events Schedule. The last visit of Study 64041575RSV2004 (ie, Day 28) may be combined with the entry visit of this LTFU study.

Parents/caregivers will be provided with a wheezing parent/caregiver card and a medication parent/caregiver card, both of which should be completed on a daily basis. These parent/caregiver cards will serve as reminder cards when a study site responsible person interviews the subject's parent/caregiver in order to complete a standardized paper questionnaire. The questionnaire will be completed by a study site responsible person at each study site visit as noted in the Time and Events Schedule and during a monthly telephone call (calendar month ±7 days) between study site visits (see Section 9.1.3).

An unblinded interim analysis will be performed when all subjects from the first season in Study 64041575RSV2004 who are enrolled in this LTFU study complete the 18 months follow-up assessment of this LTFU study. Sites and the parents/caregivers of subjects will remain blinded. This interim analysis will serve to evaluate the need for an extension of the follow-up period (see Section 11.6).

The planned total study duration for each subject will be 24 months unless the decision is taken to extend the duration of follow-up in this study, based on the interim analysis.

3.2. Study Design Rationale

This study is a LTFU study in subjects who received lumicitabine or placebo in Study 64041575RSV2004.

4. SUBJECT POPULATION

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.

4.1. Inclusion Criteria

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

1. Male or female infants and children who were previously randomized in Study 64041575RSV2004 for the treatment of RSV infection and who completed the planned course of the study drug and the last study-related visit of Study 64041575RSV2004.

2. The subject's legally acceptable representative must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing for the subject to participate in the study.

4.2. Exclusion Criteria

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

1. The subject's legally acceptable representative, ie, parent/legal guardian/caregiver, is not able to maintain reliable communication with the investigator.

2. 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.

5. TREATMENT ALLOCATION AND BLINDING

The parent/caregiver of subjects who enroll in this study and their investigators will remain blinded to the study treatment (lumicitabine or placebo) administered in the previous Study 64041575RSV2004 until the completion of this LTFU study, including any extension period.

6. DOSAGE AND ADMINISTRATION

Not applicable as no study drug will be administered in this study.

7. TREATMENT COMPLIANCE

Not applicable as no study drug will be administered in this study.

8. MEDICATIONS

There are no medication restrictions in this study.

Medication use will be monitored throughout the study from signing of the ICF until the last study-related activity. Parents/caregivers will be required to bring all medications to the study site visit. Additionally, parents/caregivers will be required to document on a daily basis use of medication on a medication parent/caregiver card (see Attachment 4), which will serve as a reminder card to be used during the study site visits and monthly phone calls between study site visits for recording the medication used for respiratory infections and illnesses on the Concomitant Medication page of the electronic case report form (eCRF) by the study site personnel.

Parents/caregivers will be required to return the completed parent/caregiver cards to the study sites every 3 months (eg, in person or by mail/email/fax when no study site visit is scheduled).

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of clinical and safety assessments.

No blood sampling will be performed in this study.

9.1.2. Entry Visit

Screening can be performed as soon as it is confirmed that the subject participated in Study 64041575RSV2004 and completed the planned course of the study drug and the last study-related visit. Subjects may be enrolled within 3 months after randomization in Study 64041575RSV2004. The last visit of Study 64041575RSV2004 (ie, Day 28) may be combined with the entry visit of this LTFU study (Study 64041575RSV2002).

At the entry visit, after signing the ICF, the overall eligibility of the subject to participate in the study will be assessed.

Baseline demographics and medical/family history from the previous Phase 2 Study 64041575RSV2004 will be captured in the LTFU (Study 64041575RSV2002) eCRF. Medical and family history to identify risk factors for wheezing/asthma at baseline, including prenatal smoking by the subject's mother, subject's exposure to tobacco smoke, wheezing associated with symptoms of acute respiratory infections, whether the subject has siblings or attends kindergarten/day care, and personal and/or family history of atopy/allergy will be recorded in the eCRF.

Parents/caregivers will be provided with the medication and wheezing parent/caregiver cards, both of which need to be completed on a daily basis (see Attachment 3 and Attachment 4).

During the entry visit, a clinical questionnaire (see Attachment 2) needs to be completed by a study site responsible person, by interviewing the subject's parent/caregiver, to collect the following information:

- Wheezing.
- Diagnosis of asthma, eczema, and allergic rhinitis. All medical information needed to confirm the diagnosis of asthma, eczema, and allergic rhinitis needs to be collected by the study site personnel.
- Impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members.

This questionnaire will capture information since the last study visit:

- If the entry visit of Study 64041575RSV2002 coincides with the last visit of Study 64041575RSV2004 (ie, Day 28), the "last study visit" in the questionnaire refers to

the Day 14 visit in Study 64041575RSV2004. Any recalled events in the questionnaire will be related to this time period.

- If the entry visit of Study 64041575RSV2002 takes place after the last visit of Study 64041575RSV2004 (ie, Day 28), the "last study visit" in the questionnaire refers to the Day 28 visit in Study 64041575RSV2004. Any recalled events in the questionnaire will be in the last 30 days or less (if the entry visit to last study visit of Study 64041575RSV2004 is less than 30 days).

9.1.3. Study Period

No study drug will be administered.

The medical follow-up of the subjects will be performed according to the local standard of care during the assessment period.

At each study site visit (3, 6, 12, 18, and 24 months after entry visit) as noted in the Time and Events Schedule and during a monthly telephone call (calendar month ±7 days), a clinical questionnaire (see Attachment 2) will be completed by a study site responsible person, by interviewing the subject's parent/caregiver, to collect the following information:

- Wheezing.

  The parent/caregiver will be provided with a wheezing parent/caregiver card to be completed daily (see Attachment 3) which will aid the site responsible person in completing the questionnaire.
- Diagnosis of asthma, eczema, and allergic rhinitis. All medical information needed to confirm the diagnosis of asthma, eczema, and allergic rhinitis needs to be collected by the study site personnel.
- Impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members.

Medical resource utilization data will be collected throughout the study.

Parents/caregivers will also be provided with a medication parent/caregiver card to record medication use on a daily basis (see Attachment 4).

Parents/caregivers will be required to return the completed wheezing and medication parent/caregiver cards to the study sites every 3 months (eg, in person or by mail/email/fax when no study site visit is scheduled).

9.2. Clinical Evaluations

The study includes the following clinical evaluations:

- Collection of information on the clinical diagnosis of asthma to determine the incidence of asthma.
- Collection of presence of wheezing on a daily basis to determine the frequency of wheezing and wheezing episodes.

- Collection of medical history and family history to identify risk factors for wheezing/asthma at baseline.
- Collection of data to determine the frequency and type of respiratory infections.
- Collection of data on medications used for the treatment of respiratory infections and illnesses (eg, bronchodilators).
- Collection of data from lung function tests and allergy tests (immunoglobulin E and skin test), if available, as supporting documentation of the diagnosis of asthma, wheezing, and atopy.

9.3. Medical Resource Utilization and Health Economics

Medical resource usage (including medical visits, emergency room visits, and hospitalizations, all for respiratory conditions) and the impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members will be collected throughout the course of the study.

9.4. Safety Evaluations

Any SAEs or reportable AEs occurring during the study must be recorded on the AE section of the eCRF.

The following AEs will be considered reportable (within the context of this study):

- Respiratory illness AEs, including subsequent RSV infections.
- AEs considered at least possibly related to lumicitabine or placebo.
- SAEs (defined in Section 12.1.1).

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

Adverse Events

Reportable AEs will be reported by the subject's parent/caregiver (or the subject's legally acceptable representative) for the duration of the study.

Any reportable AEs persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.5. Sample Collection and Handling

No safety or PK blood sampling will be performed.

10. SUBJECT COMPLETION/WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Month 24 of the assessment period (or until the last assessment, if the study is extended).

10.2. Withdrawal From the Study

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

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

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

When a subject is withdrawn by his/her parent(s)/caregiver(s) before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document.

11. STATISTICAL METHODS

Statistical analyses will be performed by a qualified vendor under the supervision/responsibility of the sponsor.

11.1. Subject Information

All subjects whose parent/caregiver provides informed consent will be included in the analysis. Demographics and other baseline characteristics will be summarized descriptively.

11.2. Sample Size Determination

No formal power calculation has been performed, as this is an LTFU study in which infants and children from the previous Phase 2 study of lumicitabine (Study 64041575RSV2004) may be enrolled.

The planned number of subjects enrolled in Study 64041575RSV2004 is up to 120 subjects on lumicitabine and up to 60 subjects on placebo. It is expected that approximately 35% of those subjects will participate in this LTFU study.

11.3. Clinical Analyses

The final analysis will be done when all the subjects have completed the last planned assessment of this LTFU study or discontinued earlier.

11.3.1. Primary Analysis

The primary endpoints in this study are the clinical diagnosis of asthma and the percentage of wheezing days in a subject within the first 2 years after the RSV infection, as reported by the parent/caregiver.

No statistical testing will be done.

Estimates of the incidence of asthma will be presented together with the 95% (2-sided) confidence interval (CI) by previous treatment group. The previous treatment group is defined as

the actual treatment of the Study 64041575RSV2004. As a sensitivity analysis, the incidence of asthma will be presented for the subgroup of subjects for whom at least 12 months of follow-up data are available.

The percentage of days with wheezing within the first 2 years after the RSV infection will be calculated per subject. Descriptive statistics, including 95% CIs, will be presented by previous treatment group.

11.3.2. Secondary Analysis

Descriptive statistics and frequency tabulations will be used to present the percentage of wheezing days per month, the mean number of wheezing episodes, and the number and type of respiratory infections by previous treatment group.

As a sensitivity analysis, 2 different imputations for missing data will be performed:

- Missing values will be replaced with the mean of the previous and subsequent month of the subject. When values at the end of the second follow-up year are missing, these missing values will be replaced by the mean of the previous month and the same month of the previous year. Thus, missing values will be replaced by values that are completely dependent on observations of the same subject.
- Missing values will be imputed by the mean of non-missing values of other subjects during the same month of the same follow-up year of the same treatment group. Thus, with this approach, missing values will be replaced by values that are independent of observations from the same subject.

11.4. Medical Resource Utilization and Health Economics Analyses

Medical resource utilization will be evaluated using frequency tabulations and listings by previous treatment group.

The impact of the subject's health status on normal daily activities for subjects, parents/caregivers, and other family members will be evaluated using frequency tabulations and listings by previous treatment group.

11.5. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify the reportable AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities. For each reportable AE and SAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by previous treatment group. In addition, comparisons between previous treatment groups will be provided if appropriate.

11.6. Interim Analysis

An unblinded interim analysis will be performed when all subjects from the first season in Study 64041575RSV2004 who are enrolled in this LTFU study complete the 18 month

follow-up assessment of this LTFU study. This interim analysis will serve to evaluate the need for an extension of the follow-up period. The interim analysis will use all available data; the results will be presented by previous treatment group, using descriptive statistics.

Based on this interim review, the study may be extended up to an additional 3 years (ie, total duration up to 5 years after randomization into Study 64041575RSV2004). In the event that the study is extended, the parents/caregivers of subjects will be required to provide additional informed consent.

Additional interim analyses may be performed for regulatory purposes.

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 AEs and SAEs

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

Note: The sponsor collects AEs starting with the signing of the ICF to the last study-related activity. In this study, only reportable AEs (respiratory illness AEs and AEs considered at least possibly related to lumicitabine or placebo) and SAEs will be recorded.

Any AEs reported in Study 64041575RSV2004 ongoing at the entry visit of this LTFU study will be considered part of the subject's medical history. If the AE worsens during this study and is a reportable AE or SAE, it will be reported as also occurring in the LTFU study.

Serious Adverse Event

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

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

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug administered in Study 64041575RSV2004 and the event (eg, death from anaphylaxis), the event must be reported as a serious unexpected suspected adverse reaction (SUSAR) 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 lumicitabine, the expectedness of an AE will be determined by whether or not it is listed in the IB.[8]

Adverse Event Associated With the Use of the Drug

An AE is considered associated (ie, at least possibly related) 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 administered in Study 64041575RSV2004.

Doubtful

An AE for which an alternative explanation is more likely, eg, medication use, 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 administered in Study 64041575RSV2004. An alternative explanation, eg, medication use, 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 administered in Study 64041575RSV2004. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, medication use, 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, medication use, 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 Division of Microbiology and Infectious Diseases (DMID) categorical descriptors; for abnormalities NOT found elsewhere in the toxicity tables (see Attachment 1) the scale below is to be used for the estimation of severity:

GRADE 1 **Mild**: Transient of mild discomfort (<48 hours); no medical intervention/therapy required.

GRADE 2 **Moderate**: Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 **Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

GRADE 4 **Life-threatening or death**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization (or hospice) care probable.

12.2. Procedures

12.2.1. All Adverse Events

All reportable AEs and SAEs 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. SAEs, including those spontaneously reported to the investigator, must be reported using the SAE Form.

All events that meet the definition of an SAE will be reported as SAEs.

All SAEs and reportable AEs 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 the study drug administered in Study 64041575RSV2004. 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 SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject's parent/caregiver 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 personnel only).
- Site number.
- Subject number.

12.2.2. Serious Adverse Events

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

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

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

- The event resolves.

- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study drug administered in Study 64041575RSV2004 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 the 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.

12.3. 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

Not applicable as no study drug will be administered in this study.

14. STUDY DRUG INFORMATION

Not applicable as no study drug will be administered in this study.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following:

- Lumicitabine IB and addenda (if applicable).
- Contact Information page(s).
- Electronic data capture manual/eCRF completion guidelines.
- Parent/caregiver card for wheezing and medications, including instructions.
- Clinical paper questionnaire, including instructions.

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

The potential subject's legally acceptable representative will be fully informed of the risks and requirements of the study and, during the study, subject's parent/caregiver 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 whose parent/caregiver is fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the subject with authority to authorize participation in research. For each subject, his or her parent (both parents, if available or if required according to local regulations) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refer to the subjects and his or her parent or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process.

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.

GCP 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 subject's parent/caregiver).
- IB (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.
- Written information provided to subject's parent/caregiver.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).
- Revision(s) to ICF and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug administered in Study 64041575RSV2004.
- 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 Form

Each 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 the reviewing IEC/IRB, and be in a language that the parent/caregiver 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 the parent/caregiver of 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' legally acceptable representatives will be informed that subject 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. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of LTFU, 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's 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's legally acceptable representative agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

If the subject's 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's legally acceptable representative is obtained.

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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.

Waivers for inclusion and exclusion criteria are not permitted.

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 the first study procedure:

- 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 study 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).

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. In cases where the subject is not randomized into the study, the date seen and date of birth 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 clinical evaluation parameters as required by the protocol; record of all SAEs and reportable AEs; medication; and date of study completion and reason for early withdrawal from the study, if applicable.

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

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

Data collected during the phone calls and study site visits can be recorded directly into the eCRF and the paper questionnaire, and will be considered the source data.

17.5. Case Report Form Completion

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

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

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

All subjective measurements 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. Parent/Caregiver

The subject's parent/caregiver with routine and frequent experience caring for the subject will provide information about the subject's status and symptoms and all other information required during clinical interviews conducted by the study site responsible person at the time points noted in the Time and Events Schedule.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor will review eCRFs 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.

17.7. 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, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be

retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

17.8. 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, including but not limited to, the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment (including any extension period) 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 assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. 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.
- Discontinuation of further study drug development.

17.10. 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.

17.11. Use of Information and Publication

All information, including but not limited to, information regarding lumicitabine 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 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 lumicitabine, 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 any 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 design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (November 2007)

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

ABBREVIATIONS: Abbreviations utilized in the table:

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

ESTIMATING SEVERITY GRADE

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

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

* The draft DMID pediatric toxicity tables characterize death as a Grade 5 event, for the purposes of this study the sponsor will categorize events into 4 grades and has included death with life-threatening in the Grade 4 category.

SERIOUS OR LIFE-THREATENING ADVERSE EVENTS

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, and 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 WHO) have been adapted for use by the DMID and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.

- Criteria are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

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

(Selected values for children less than or equal to 3 months of age – does not apply to preterm infants)

For all parameters not listed in this table, please refer to the DMID Toxicity Table for children >3 months of age

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin				
1-7 days old	13.0 - 14.0 g/dL	12.0 - 12.9 g/dL	<12 g/dL	Cardiac failure secondary to anemia
8-21 days old	12.0 - 13.0 g/dL	10.0 - 11.9 g/dL	<10.0 g/dL	Cardiac failure secondary to anemia
22-35 days old	9.5 - 10.5 g/dL	8.0 - 9.4 g/dL	<8.0 g/dL	Cardiac failure secondary to anemia
36-60 days old	8.5 - 9.4 g/dL	7.0 - 8.4 g/dL	<7.0 g/dL	Cardiac failure secondary to anemia
61-90 days old	9.0 - 9.9 g/dL	7.0 - 8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anemia
Absolute Neutrophil Count				
1 day old	5000 - 7000/mm^3	3000 - 4999/mm^3	1500 - 2999/mm^3	<1500/mm^3
2-6 days old	1750 - 2500/mm^3	1250 - 1749/mm^3	750 - 1249/mm^3	<750/mm^3
7-60 days old	1200 - 1800/mm^3	900 - 1199/mm^3	500 - 899/mm^3	<500/mm^3
61-90 days old	750 - 1200/mm^3	400 - 749/mm^3	250 - 399/mm^3	<250/mm^3

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

(Selected values for children younger than or aged 3 months)

HEMATOLOGY (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (fractionated bilirubin test must be performed when total bilirubin is elevated)				
<7 days old	-	20 - 25 mg/dL	26 - 30 mg/dL	>30 mg/dL
7-60 days old	1.1-1.9xN	2.0 - 2.9xN	3.0 - 7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0 - 2.9xN	3.0 - 7.5xN	>7.5xN
Creatinine				
<7 days old	1.0 - 1.7 mg/dL	1.8 - 2.4 mg/dL	2.5 - 3.0 mg/dL	>3.0 mg/dL
7-60 days old	0.5 - 0.9 mg/dL	1.0 - 1.4 mg/dL	1.5 - 2.0 mg/dL	>2.0 mg/dL
61-90 days old	0.6 - 0.8 mg/dL	0.9 - 1.1 mg/dL	1.2 - 1.5 mg/dL	>1.5 mg/dL
Creatinine Clearance				
<7 days old	35 - 40 mL/min	30 - 34 mL/min	25 - 29 mL/min	<25 mL/min
7-60 days old	45 - 50 mL/min	40 - 44 mL/min	35 - 39 mL/min	<35 mL/min
61-90 days old	60 - 75 mL/min	50 - 59 mL/min	35 - 49 mL/min	<35 mL/min
Hypocalcemia				
<7 days old	6.5 - 6.9 mEq/L	6.0 - 6.4 mEq/L	5.5 - 5.9 mEq/L	<5.5 mEq/L
7-60 days old	7.6 - 8.0 mEq/L	7.0 - 7.5 mEq/L	6.0 - 6.9 mEq/L	<6.0 mEq/L
61-90 days old	7.8 - 8.4 mEq/L	7.0 - 7.7 mEq/L	6.0 - 6.9 mEq/L	<6.0 mEq/L
Hypercalcemia				
<7 days old	12.0 - 12.4 mEq/L	12.5 - 12.9 mEq/L	13.0 - 13.5 mEq/L	>13.5 mEq/L
7-60 days old	10.5 - 11.2 mEq/L	11.3 - 11.9 mEq/L	12.0 - 13.0 mEq/L	>13.0 mEq/L
61-90 days old	10.5 - 11.2 mEq/L	11.3 - 11.9 mEq/L	12.0 - 13.0 mEq/L	>13.0 mEq/L

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

(Older than 3 months of age)

LOCAL REACTIONS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Induration	<10 mm	10 - 25 mm	26 - 50 mm	>50 mm
Erythema	<10 mm	10 - 25 mm	26 - 50 mm	>50 mm
Edema	<10 mm	10 - 25 mm	26 - 50 mm	>50 mm
Rash at injection site	<10 mm	10 - 25 mm	26 - 50 mm	>50 mm
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching at injection extremity and other sites	Itching over entire body

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin for children older than 3 months and younger than 2 years of age	9.0 - 9.9 g/dL	7.0 - 8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anemia
Hemoglobin for children older than 2 years of age	10 - 10.9 g/dL	7.0 - 9.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anemia
Absolute Neutrophil Count	750 - 1200/mm^3	400 - 749/mm^3	250 - 399/mm^3	<250/mm^3
Platelets	-------	50,000 - 75,000/mm^3	25,000 - 49,999/mm^3	<25,000/mm^3
Prothrombin Time (PT)	1.1 - 1.2 x ULN	1.3 - 1.5 x ULN	1.6 - 3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1 - 1.6 x ULN	1.7 - 2.3 x ULN	2.4 - 3.0 x ULN	>3.0 x ULN

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

(Older than 3 months of age)

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 - 1.75 x ULN	>1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
Pancreatic amylase	1.1 - 1.4 x ULN	1.5 - 1.9 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
Uric acid	7.5 - 9.9 mg/dL	10 - 12.4 mg/dL	12.5 - 15.0 mg/dL	>15.0 mg/dL
CPK	See neuromuscular toxicity			
Appetite	-	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Abdominal pain	Mild	Moderate - no treatment needed	Moderate - treatment needed	Severe - hospitalized for treatment
Diarrhea	Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater that 4x the amount or number normal for this child	Liquid stools greater than 8x the amount or number normal for this child

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

(Older than 3 months of age)

GASTROINTESTINAL (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Constipation	Slight change in the consistency/ frequency of stool	Hard, dry stools with a change in frequency	Abdominal pain	Distention and vomiting
Nausea	Mild	Moderate - decreased oral intake	Severe - little oral intake	Unable to ingest food or fluid for more than 24 hours
Vomiting	1 episode/day	2-3 episodes/day	4-6 episodes/day	Greater than 6 episodes per day or intractable vomiting

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

(Older than 3 months of age)

ELECTROLYTES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
CREATININE				
3 months - 2 years of age	0.6 - 0.8 x ULN	0.9 - 1.1 x ULN	1.2 - 1.5 x ULN	>1.5 x ULN
2 years - 12 years of age	0.7 - 1.0 x ULN	1.1 - 1.6 x ULN	1.7 - 2.0 x ULN	>2.0 x ULN
Older than 12 years of age	1.0 - 1.7 x ULN	1.8 - 2.4 x ULN	2.5 - 3.5 x ULN	>3.5 x ULN
Hypernatremia	-	<145 - 149 mEq/L	150 - 155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia	-	130 - 135 mEq/L	129 - 124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0 - 5.9 mEq/L	6.0 - 6.4 mEq/L	6.5 - 7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0 - 3.5 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5 - 11.2 mg/dL	11.3 - 11.9 mg/dL	12.0 - 12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.0 - 6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2 - 1.4 mEq/L	0.9 - 1.1 mEq/L	0.6 - 0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55 - 65 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116 - 159 mg/dL	160 - 249 mg/dL	250 - 400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150 - 499 mg/day	3+ or 500 - 1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	----	Gross hematuria

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

(Older than 3 months of age)

ELECTROLYTES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypernatremia	-	<145 - 149 mEq/L	150 - 155 mEq/L	>155 mEq/L or abnormal sodium AND mental status changes
Hyponatremia	-	130 - 135 mEq/L	129 - 124 mEq/L	<124 mEq/L or abnormal sodium AND mental status changes
Hyperkalemia	5.0 - 5.9 mEq/L	6.0 - 6.4 mEq/L	6.5 - 7.0 mEq/L	>7.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypokalemia	3.0 - 3.5 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L	<2.0 mEq/L or abnormal potassium AND cardiac arrhythmia
Hypercalcemia	10.5 - 11.2 mg/dL	11.3 - 11.9 mg/dL	12.0 - 12.9 mg/dL	>13.0 mg/dL
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.0 - 6.9 mg/dL	<6.0 mg/dL
Hypomagnesemia	1.2 - 1.4 mEq/L	0.9 - 1.1 mEq/L	0.6 - 0.8 mEq/L	<0.6 mEq/L or abnormal magnesium AND cardiac arrhythmia
Hypoglycemia	55 - 65 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL or abnormal glucose AND mental status changes
Hyperglycemia	116 - 159 mg/dL	160 - 249 mg/dL	250 - 400 mg/dL	>400 mg/dL or ketoacidosis
Proteinuria	Tr-1+ or <150 mg/day	2+ or 150 - 499 mg/day	3+ or 500 - 1000 mg/day	4+ or Nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic >25 cells/hpf	-	Gross hematuria

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

(Older than 3 months of age)

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

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

(Older than 3 months of age)

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

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

(Older than 3 months of age)

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

Attachment 2: Standardized Paper Questionnaire for Use During Scheduled Study Site Visits and Monthly Phone Calls Between Study Site Visits

A Long-term Follow-up of Study 64041575RSV2004 to Evaluate the Impact of Lumicitabine on the Incidence of Asthma and/or Wheezing in Infants and Children with a History of Respiratory Syncytial Virus Infection

Protocol Number: 64041575RSV2002

Standardized Questionnaire for Use During Scheduled Study Site Visits and Monthly Phone Calls Between Study Site Visits

General Instructions for the Study Site

- The questionnaire needs to be completed in its entirety by the study site through parent/caregiver interviews during scheduled study site visits (entry visit, 3, 6, 12, 18, and 24 months) and monthly phone calls between study site visits.
- When referring to wheezing, eczema, and allergic rhinitis with the parent/caregiver, please use simple terminology provided in the definitions section (see below).
- Records need to be obtained from the subject's doctor or health care provider to confirm the diagnosis of asthma, eczema, and allergic rhinitis.
- Please keep completed questionnaires and wheezing/medication parent/caregiver cards as part of the study file.

Definitions

Wheezing: whistling sounds in the chest

Eczema: dry, itchy, scaly patches on the skin

Allergic rhinitis: inflammation of the nasal passages due to allergies

Date of current interview: **__/__/____ (DD/MM/YYYY)**

Patient ID: **_____**

Section A: Questions About Wheezing

Definition of wheezing: whistling sounds in the chest

Please remind the parent/caregiver that the date of last interview was:

__/__/____ (DD/MM/YYYY)

1. Since the last study site visit/telephone call, did the child have any wheezing?

☐ No ⟶ go straight to Section B

☐ Yes

a. Please provide the days of wheezing and missing days of wheezing in the calendar below.

____/_____ (Month/Year)						
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**

Section B: Questions About Asthma

Important note for the study site: If on a previous questionnaire, the parent/caregiver indicated that the child has been diagnosed with asthma, please proceed to Section C.

Please remind the parent/caregiver that the date of last interview was:

__/__/____ (DD/MM/YYYY)

1. **Since the last study site visit/telephone call, has the child been diagnosed with asthma by a doctor or health care provider?**

   ☐ No
   ☐ Yes

   a. **When was the child diagnosed with asthma by a doctor or health care provider?**
      Date of asthma diagnosis: __/__/____ (DD/MM/YYYY)

Section C: Questions About Eczema

Important note for the study site: If on a previous questionnaire, the parent/caregiver indicated that the child has been diagnosed with eczema, please proceed to Section D.

Definition of eczema: dry, itchy, scaly patches on the skin

Please remind the parent/caregiver that the date of last interview was:

__/__/____ (DD/MM/YYYY)

1. **Since the last study site visit/telephone call, has the child been diagnosed with eczema by a doctor or health care provider?**

   ☐ No
   ☐ Yes

   a. **When was the child diagnosed with eczema by a doctor or health care provider?**
      Date of eczema diagnosis: __/__/____ (DD/MM/YYYY)

Section D: Questions About Allergic Rhinitis

Important note for the study site: If on a previous questionnaire, the parent/caregiver indicated that the child has been diagnosed with allergic rhinitis, please proceed to Section E.

Definition of allergic rhinitis: inflammation of the nasal passages due to allergies and characterized by episodes of sneezing, stuffy nose, often accompanied by itching of the eyes and nose.

Please remind the parent/caregiver that the date of last interview was:

__/__/____ (DD/MM/YYYY)

1. **Since the last study site visit/telephone call, has the child been diagnosed with allergic rhinitis by a doctor or health care provider?**

   ☐ No
   ☐ Yes

   a. **When was the child diagnosed with allergic rhinitis by a doctor or health care provider?**
      Date of allergic rhinitis diagnosis: __/__/____ (DD/MM/YYYY)

Section E: Questions of the Impact of the Child's Health on the Parent/Caregiver and Family

1. **Is the parent/caregiver currently in paid employment?**

☐ No

   a. **Is the parent/caregiver currently not employed because of the child's health problems?**

      ☐ No

      ☐ Yes

☐ Yes

   a. **Since the date of the last study site visit/telephone call, how many days did the parent/caregiver miss from work because of the child's health problems?**

      Total number of days missed from work because of the child's health problems: ____ days

   b. **Since the date of the last study site visit/telephone call, how much did the child's health problems affect the ability of the parent/caregiver to be productive on the job (eg, complete tasks on time, get to work on time, pay attention when at work)? If your child's health, affected work only a little, instruct the parent/caregiver to choose a low number. Please circle a number below based on the response from parent/caregiver.**

Child's health had no effect on parent's/caregiver's work productivity	0	1	2	3	4	5	6	7	8	9	10	Child's health completely prevented the parent/caregiver from being productive at work

2. **Since the date of the last study site visit/telephone call, how much has the child's health problems affected the parent's/caregiver's availability to perform normal daily activities (other than work for pay)? By normal daily activities we mean the usual activities you perform, such as working around the house, gardening, shopping, childcare, exercising, studying, etc. If the child's health problem affected activities only a little, instruct the parent/caregiver to choose a low number. Please circle a number below based on the response from parent/caregiver.**

Child's health had no effect on parent's/caregiver's normal daily activities	0	1	2	3	4	5	6	7	8	9	10	Child's health completely prevented parent/caregiver from doing normal daily activities

3. **Since the date of the last study site visit/telephone call, how much has the child's health affected the child's usual activities? If the child's health had little effect on the child's usual activities, instruct the patient/caregiver to choose a low number. Please circle a number below based on the response from parent/caregiver.**

Child's health had no effect on the child's usual activities	0	1	2	3	4	5	6	7	8	9	10	Child's health severely limited the child's usual activities

4. **Since the date of the last study site visit/telephone call, how much has the child's health affected the parent's/caregiver's health? If the child's health problem had little effect on the parent's/caregiver's health, instruct the patient/caregiver to choose a low number. Please circle a number below based on the response from parent/caregiver.**

Child's health had no effect on the parent's/caregiver's health	0	1	2	3	4	5	6	7	8	9	10	Child's health caused severe health problems for the parent/caregiver

5. **Since the date of the last study site visit/telephone call, has the child's health made it difficult for the caregiver to care for other family members?**
   - □ No
   - □ Yes

6. **Since the date of the last study site visit/telephone call, how often did the child's health limit the amount of time the parent/caregiver spent with other family members?**
   - □ Rarely or never limited time
   - □ Occasionally limited time
   - □ Often limited time
   - □ Most of the time or always limited time

7. **Since the date of the last study site visit/telephone call, how many days did other family members miss from work because of the child's health problems (eg, to stay home to care for the child or other family members, to take time off to take the child for medical visits, etc.)?**
   Total number of days that family members missed from work because of the child's health problems: ____ days

General Reminders for the Parent/Caregiver for the Next Study Site Visit/Telephone Call

- Please remind the parent/caregiver to bring all medications and medication card to the scheduled study site visits and telephone calls in order to be able to capture the medication history.
- Please remind the parent/caregiver to bring the wheezing card to the scheduled study site visits and telephone calls in order to be able to capture the days of wheezing.
- Please remind the parent/caregiver to bring the wheezing and medication card every 3 months to the site according to local procedures (eg, by mail, by scan/email, in person, etc.).

End of questionnaire

Attachment 3: Wheezing Parent/Caregiver Card to Be Completed Daily

FRONT

Wheezing card for: _____ (name of the child)

January 2018						
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

BACK

How to use the wheezing card

- This card is to help you remember which days your child had wheezing; that is a day when you heard whistling sounds in the child's chest during breathing.
- Each day at bedtime:
  - If the child had wheezing that day, put a "1" in the box for the date.
  - If the child did not have wheezing that day, put a "0" in the box for the date.

How to read the wheezing card during the phone calls with the study coordinator

- Provide the days the child had wheezing since the last study site visit/phone call.
- Provide the days the child had no wheezing since the last study site visit/phone call.

Please bring <u>all wheezing cards</u> with you to the study site visits/phone calls! Please also bring the wheezing cards every 3 months to the study site according to local procedures (eg, by mail, by scan/email, in person, etc.)!

In case of questions about the study or the wheezing card, please call:

- Name: _____
- Phone number: _____

Attachment 4: Medication Parent/Caregiver Card to Be Completed Daily

FRONT

Medication card for: _____ (name of the child)

Medication (Generic Name)	Indication	Route	Dose	Strength	Frequency	Start date (DD/MM/YYYY)	Stop date (DD/MM/YYYY)

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BACK

How to use the medication card

- Write all medications prescribed to your child
- For each medication, you need to include the medication name (generic name), indication, route, dose, strength, frequency, start date and stop date.
  - The indication represents the reason for treatment (for example wheezing, asthma, eczema, allergic rhinitis, headache, etc.).
  - The route represents the way the medication is administered to your child (for example oral, inhaled [administered by mask], topical [applied on skin], etc.).
  - The dose represents the number of pills, capsules, puffs, milliliter, teaspoons, tablespoons, etc. that your child has to take every time the medication is given to your child (for example, 2 pills, 5 mililiters, 1 teaspoon).
  - The strength represents the amount (for example, how many mg) per pill, capsule, milliliter, etc. (for example, 20 mg pill, or 15 mg per milliliter).
  - The frequency represents how often the medication is to be given to your child (for example, every 8 hours, every 12 hours, once a day, etc.).
  - The start date represents the date when the first dose was given to your child.
  - The stop date represents the date when the last dose was given to your child.
- Use one medication card per calendar month.
  - If your child has been prescribed many medications in a given month, please use the necessary number of medication cards in order to collect all the medications.

Please bring all medications and all medication cards with you to the study site visits/phone calls! Please also bring the medication cards every 3 months to the study site according to local procedures (eg, by mail, by scan/email, in person, etc.) !

In case of questions about the study or the medication card, please call:

- Name: _____
- Phone number: _____

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Guy De La Rosa

Institution: Janssen Research & Development

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

(Day Month Year)

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

SIGNATURES

Signed by	Date	Justification
Guy De la rosa	31Jan2018, 07:18:42 AM, UTC	Document Approval