Janssen Research & Development

Statistical Analysis Plan

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

Lumicitabine (JNJ-64041575, ALS-008176)

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

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AMENDMENT HISTORY

Not applicable.

ABBREVIATIONS

AE	adverse event
BMI	body mass index
CI	confidence interval
eCRF	electronic case report form
LTFU	long-term follow-up
MedDRA	medical dictionary for regulatory activities
PRESORS	pediatric RSV electronic severity and outcomes rating scale
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
WHO-DD	World Health Organization drug dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for the analysis of safety for the final analysis of Study 64041575RSV2002 and should be considered in conjunction with the clinical trial protocol.[2]

1.1. Trial Objectives

Primary Objectives
The primary objectives are to evaluate in infants and children who have been treated with lumicitabine or placebo in Study 64041575RSV2004[1] 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.

1.2. Trial 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 (i.e., 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 randomization in Study 64041575RSV2004. The last visit of Study 64041575RSV2004 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.

More details can be found in the Time-and-Event schedule in the study protocol.

1.3. Statistical Hypotheses for Trial Objectives

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.

1.4. Sample Size Justification

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 was expected that approximately 35% of those subjects were to participate in this LTFU study.

1.5. Randomization and Blinding

Randomization is not applicable in this study since it is the LTFU of Study 64041575RSV2004.

The parent/caregiver of subjects who enroll in this study and their investigators were to 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.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows and Phase definition

As this is a LTFU of Study 64041575RSV2004, only 1 analysis phase will be defined (see Table 1). The reference is the date of informed consent in study 64041575RSV2002.

Table 1: Trial Phase

Trial Phase	Trial Phase (Numeric Version)	Start Date	End Date
Long Term Follow Up	1	00:00 of the date of signing the informed consent	Trial termination date (date of last contact) with timestamp 23:59

For assigning assessments, the visit schedule as reported in the database will be used.

If a subject has a missing visit, the data will be set to missing and will not be imputed. Information of an unscheduled visit will be merged with the scheduled visit, meaning that any information will be added to scheduled visit data.

2.2. Pooling Algorithm for Analysis Centers

No pooling algorithm for analysis centers will be specified.

2.3. Analysis Sets

2.3.1. All Enrolled Analysis Set

The All Enrolled analysis set includes all subjects who were enrolled in this LTFU study. The All Enrolled set will be analyzed as treated.

2.4. Definition of Subgroups and Subsets

As study 64041575RSV2002 only included 7 subjects, no subgroups or subsets will be defined.

2.5. Study Day and Relative Day

The reference day is the date of informed consent in study 64041575RSV2002. All assessments will be assigned a day relative to this day.

The relative day for a visit is defined as:

Visit day - (informed consent in study 64041575RSV2002) +1

For the monthly reports, the visit schedule will be based on the entry dates of each monthly report; the entry of the first report is the Screening visit, and each subsequent entry is considered as the next Monthly report (starting with Month 2, reflecting the time since the RSV event).

2.6. Baseline

The baseline as defined in study 64041575RSV2004 will be used in the presentation of demographics and disease characteristics. A footnote will indicate that the data are used from study 64041575RSV2004.

3. INTERIM ANALYSIS

An unblinded interim analysis was to 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 was to serve an evaluation of the need for an extension of the follow-up period. The interim analysis was not performed as the project was stopped and due to the limited sample size, an extension of the follow-up period was not deemed useful for the objectives of this trial.

4. SUBJECT INFORMATION

Subject information will be analyzed on the All Enrolled set, defined as the subjects that enrolled in the 64041575RSV2002 study (i.e., signed informed consent).

4.1. Demographics and Baseline Characteristics

In this study (where no treatment is given), treatment will be used in summaries, where the treatment of RSV2004 will be presented. All demographics and baseline characteristics will be summarized overall and by treatment group. Descriptive statistics and frequency distribution will be provided for respectively the continuous and categorical parameters below. These data will be taken for the All Enrolled set from the data of the 64041575RSV2004 study, and at the time of enrollment in that study (eg age reported here is the age at the time of the index event).

Demographic parameters [to be inherited from the 64041575RSV2004 study]:

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander). If multiple race categories are indicated, the Race is recorded as 'Multiple'.
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- Geographic region (based on country: North America [to include Puerto Rico], Europe, South America, Asia-Pacific)
- Region (Japan, non-Japan) Note: Japan region only includes subjects indicated as Japanese on the eCRF.
- Age (months)
- Age category [≥28 days to <24 months, ≥24 to <=36 months]
- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2) = Weight at baseline (kg) / (Height at baseline (m))^2 (rounded to 1 decimal)
- Gestational age at birth (Weeks)
- Prenatal smoking by the mother (yes, no)
- Exposure to tobacco smoke at home (yes, no)
- Contact with other children (yes, no)
- Attending day care (yes, no)
- Breastfeeding (yes, no)

Baseline disease characteristics

- Wheezing associated with symptoms of acute respiratory infections (yes, no)
- Personal or family history of atopy/allergy (yes, no)

[to be inherited from the 64041575RSV2004 study]:

- Duration of RSV symptoms from onset till time of randomization (days)
- Duration of RSV symptoms from onset till time of randomization (days) categories (≤3 days; >3 days to ≤5 days)
- Presence comorbid conditions (yes, no)
- Number of subjects with one of following comorbid conditions:
    - prematurity at birth [subject's gestational age was <37 weeks; for infants <1 year old at randomization],
    - bronchopulmonary dysplasia,
    - congenital heart disease,
    - other congenital diseases,
    - Down syndrome,
    - neuromuscular impairment, or
    - cystic fibrosis
- Baseline RSV subtype (Type A, Type B, Type A+B)
- Receiving Supplemental Oxygen (yes, no)
- Reasons for hospitalization (PRESORS question 1)

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects who completed and discontinued the trial, with the reasons of discontinuation
- Subjects per analysis visit in the trial

4.3. Protocol Deviations

Only major protocol deviations will be defined in this trial. All major protocol deviations will be listed, including the deviations to the inclusion-exclusion criteria, and the violations to the prohibitions and restrictions, if any. A tabulation of the number and percentage of subjects per major protocol deviation will be provided.

4.4. Medications

Medications will be coded using the [World Health Organization Drug Dictionary (WHO-DD)] in the version current at database lock. Summaries of medications (number and percent of subjects) will be presented by treatment group.

4.5. Preplanned Surgeries/Procedures

A tabulation and listing of the preplanned surgeries/procedures requiring hospitalization will be made.

5. EFFICACY

5.1. Primary Efficacy Endpoint(s)

5.1.1. Definition

The primary endpoints are:

1. Clinical diagnosis of asthma within the first 2 years after the RSV infection, as diagnosed by a physician and reported by the parent/caregiver. This will be derived based on the completed study questionnaires at each visit/telephone call until the final visit. It is either "Yes" or "No".
2. The percentage of wheezing days in a subject within the first 2 years after the RSV infection will be calculated as:

$$\text{Percentage of wheezing days} = \left(\frac{\text{number of wheezing days}}{\text{day of study completion} - \text{day of informed consent} + 1}\right) * 100$$

The percentage will be rounded to the nearest integer. Number of wheezing days is the sum of all days that were reported in the Monthly visit reports. The day of informed consent is the informed consent of the RSV2002 study.

5.1.2. Estimand

The incidence of asthma will be evaluated descriptively as the difference in proportions of subjects with clinical diagnosis within the first 2 years after the RSV infection for the lumicitabine versus the placebo treatment.

5.1.3. Analysis Methods

The proportions of subjects with clinical diagnosis of asthma within the first 2 years after the RSV infection will be presented descriptively by previous treatment group, together with the 95% (2-sided) confidence intervals using the Wilson method.

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

5.2. Major Secondary Endpoints

5.2.1. Definition

The definitions of these endpoints are given in Table 2. While the clinical trial protocol mentions two methods for imputing missing data, these methods will not be performed as based on the limited number of subjects enrolled in the study these analyses would not be meaningful.

Consecutive wheezing episodes will be combined.

Step 1: Combination of wheezing episodes

Consecutive wheezing episodes are defined as episodes of the same subject with the start date of an episode is exactly 1 day after the end date of the preceding episode (or same date). Wheezing

episodes can only be combined into one and the same episode if the start and stop dates are complete.

Step 2: Allocation of wheezing episodes to intervals. For analysis of incidence over time the wheezing episodes will be allocated into the analysis visits (intervals), using the start date of the episode. For the analysis of prevalence over time, the wheezing episodes will be counted in each interval it overlaps, using the available start and end date information.

Table 2: Calculations (Secondary Endpoints)

Parameter	Definition
Percentage of wheezing days per month	Percentage of wheezing days per month as based on Visit variable in the database using information reported by the parent/caregiver. The nominator is the number of Days reported in that period with wheezing, using last day – first day + 1 for reported days of wheezing. The fraction is multiplied by 100% and rounded to the nearest integer.
Number of wheezing episodes per month	Number of wheezing episodes during each month, after combination of the consecutive episodes, as based on information reported by the parent/caregiver. A wheezing episode is defined as the presence of wheezing for ≥1 day that started during the episode. If an episode is present but started in the previous episode it will not be counted.
Number of wheezing episodes within the first 2 years after the RSV infection	Number of wheezing episodes recorded between informed consent and the last day in the trial for completed subjects. It is the sum of the number of wheezing episodes across Months.
Incidence of reportable AEs and SAEs, including AEs related to respiratory illnesses and AEs considered at least possibly related to lumicitabine or placebo by the investigator.	These incidences are defined as the number of AEs overall and by category divided by the 2 year reporting period. Each AE is counted as reported. The unit will be 'per month/during the first 2 years'. In case the subject did not report on the full 24 months the divisor will be adapted to nearest number of months participating.
Number of respiratory infections per subject during study participation	The total number of respiratory infections of each subject. The unit will be 'during study participation'. The respiratory infection AE terms (AEDECOD) will be determined based on medical review and reported overall and by Preferred Term.
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.	Total number of medical visits, emergency room visits, and hospitalizations, as reported by the parent/caregiver. The number will be given overall and by relationship to respiratory conditions, as based on medical review.

5.2.2. Analysis Methods

Descriptive statistics will be used to present the percentage of wheezing days and the number of wheezing episodes per Month. Frequency tabulations will be used to summarize the number and type of respiratory infections per subject by previous treatment group.

Listings will be provided showing the reported information on wheezing and respiratory infections together with the derived efficacy parameters above. A summary will be provided for respiratory infections:

- any respiratory infections,
- serious respiratory infections,
- deaths due to respiratory infections,
- respiratory infections by toxicity grade,
- respiratory infections at least possibly related to study medication,
- serious respiratory infections that were at least possibly related to study medication

Listings will be provided for all respiratory infections.

5.3. Exploratory Endpoints

5.3.1. Definition

For the exploratory endpoints the data will be presented using for each subject a row for each month (based on the assignment in the database), and columns presenting the data to each subsequent question of the interview.

The same lay-out will be used to provide summary statistics for endpoints as defined below by treatment group and study Month. The definitions of these endpoints are given in Table 3. Parameters will be assigned to the monthly visits based on the assignment in the database.

Table 3: Calculations and Conversion Formulae (Exploratory Endpoints)

Measurement	Calculation
Subject's daily activities limited by the subject's health per Month	The parent/caregiver reports that they are not working due to the child's health problems. The answer to Questionnaire section E question 1. The result will be either "Yes" or "No" and will be calculated for Screening and each Month as based on the assignment in the database.
Percentage of days per Month the parent/caregiver missed from work due to the subject's health	This is only calculated for parents/caregivers that were working, OR not working due to the child's health problems. If the parent is not working due to the child's health problems this is set to 100%. In all other cases total number of days missed from work because of the child's health problems, divided by the end date - start date +1 of the reported Month x100% and rounded to the nearest integer. The answer to Questionnaire section E question 1.
Parent's/caregiver's productivity at work limited by the subject's health per Month	This is only calculated for parents/caregivers that were working. The extent to which the parent's/caregiver's productivity while at work was limited by the subject's health per Month. The answer to Questionnaire section E question 1b.
Subject's health problems limited the parent's/caregiver's ability to engage in normal daily activities per Month	The extent to which the subject's health problems limited the parent's/caregiver's ability to engage in normal daily activities per Month. The answer to Questionnaire section E question 2.
How much the child's health has affected the child's usual activities per Month	The extent to which the child's health affected the child's usual activities per Month. The answer to Questionnaire section E question 3.
Impact of the subject's health problems on the parent's/caregiver's health per Month	The extent to which the subject's health problems impacted the parent's/caregiver's health per Month. The answer to Questionnaire section E question 4.
Inability of the parent/caregiver to care for other family members due to the subject's health per Month	The inability of the parent/caregiver to care for other family members due to the subject's health per Month. The answer to Questionnaire section E question 5. The result will be either "Yes" or "No".
Subject's health limited the parent's/ caregiver's time spent with other family members each Month	The extent to which the subject's health limited the parent's/caregiver's time spent with other family members each Month.

	The answer to Questionnaire section E question 6. The result will be categorical as listed in the Questionnaire.
Percentage of days other family members missed from work due to the subject's health problems per Month	The percentage of days each Month that other family members missed from work due to the subject's health problems. Derived base on the Questionnaire section E question 7. Calculated as the number of days as recorded in question 7 divided by the number of days since the last study visit/telephone call. For subjects currently not in paid employment, the value will be 100% for parents/caregivers who were not employed due to the child's health problem and missing if this was not due the child's health problem.
Clinical diagnosis of eczema within the first 2 years after the RSV infection	Clinical diagnosis of eczema within the first 2 years after the RSV infection, as diagnosed by a physician and reported by the parent/caregiver. The result will be either "Yes" or "No". Derived based on the answer to Questionnaire section C until the Month 24 analysis visit.
Clinical diagnosis of allergic rhinitis within the first 2 years after the RSV infection	Clinical diagnosis of allergic rhinitis within the first 2 years after the RSV infection, as diagnosed by a physician and reported by the parent/caregiver. The result will be either "Yes" or "No". Derived based on the answer to Questionnaire section D until the Month 24 analysis visit.

5.3.2. Analysis Methods

Descriptive statistics and frequency tabulations will be used to present the parameters of long-term impact of RSV and its treatment with lumicitabine or placebo by previous treatment group at each analysis visit. For parameters that have continuous results (where the result is based on a scale from 0 to 10) descriptive statistics will be used, for the parameters with categorical results frequency tabulation will be used. The results will be presented graphically over time (mean for continuous parameters, stacked bar charts for categorical parameters).

Clinical diagnosis of eczema and allergic rhinitis within the first 2 years after the RSV infection per treatment group will be presented together with the 95% (2-sided) Wilson confidence intervals.

Listings will be provided for the parameters of long-term impact of RSV and its treatment with lumicitabine or placebo for each subject. Listings will also be provided for the clinical diagnosis of eczema and allergic rhinitis within the first 2 years after the RSV infection for each subject.

6. SAFETY

6.1. Reportable Adverse Events

6.1.1. Definitions

A reportable AE was defined in the protocol as a respiratory illness AE and/or an AE considered at least possibly related to study drug that was administered in study 64041575RSV2004 (lumicitabine or placebo), or a serious AE (SAE).

Information on eczema and allergic rhinitis was also asked to be collected in the questionnaire and has been collected as AEs. These will also be presented as reportable AEs. AEs that were reported but do not seem to fit the definition will be reported as *other*.

Reportable AEs will be categorized as:

- respiratory illness AE
- eczema
- allergic rhinitis
- other

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Events are looked at on the level of their preferred term.

6.1.2. Analysis Methods

A summary by treatment and overall of number of subjects with at least one event will be provided for the following reportable adverse events:

- any reportable adverse events,
- respiratory illness,
- eczema,
- allergic rhinitis,
- other,
- serious adverse events,
- reportable adverse events by toxicity grade,
- reportable AEs at least possibly related to study medication administered in study 64041575RSV2004,
- serious reportable adverse events that were at least possibly related to study medication administered in study 64041575RSV2004.

Tabulations will be reported by treatment and overall by category for the number of events experienced by a subject. A tabulation by system organ class and preferred term will be generated.

Listings will be provided for at least the following categories: all reportable AEs, serious AEs, reportable AEs leading to death, grade 3-4 reportable AEs, complications related to the RSV experienced during study 64041575RSV2004 (sorted by type of complication).

7. MEDICAL RESOURCE UTILIZATION

7.1. Definition

The following parameter will be considered:

Table 4: Calculations and Conversion Formulae (Medical Resource Utilization)

Measurement	Formula
Medical encounters: number of medical visits	The number of medical encounters due to respiratory conditions for each visit, derived from the eCRF overall and by type of medical encounter (as recorded). Counted as the number of unique medical encounters per subjects based on the unique combinations of the medical encounter start date and type of medical encounter.
Medical encounters: number of emergency room visits	The number of emergency room visits due to respiratory conditions for each visit, derived from the eCRF when type of medical encounter equals to emergency room.
Medical encounters: number of hospitalizations	The number of hospitalizations due to respiratory conditions for each visit, derived from the eCRF when type of medical encounter equals to hospital inpatient department, intensive care unit or Hospice/Palliative Care Unit.

7.2. Analysis Methods

Frequency tabulation will be used to summarize the number of medical encounters by categories and type of medical encounters per month by previous treatment group. A listing will be provided for the medical encounter records of each subject.

REFERENCES

1. Clinical Trial Protocol 64041575RSV2004, “A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetics of Orally Administered Lumicitabine (JNJ-64041575) Regimens in Hospitalized Infants and Children Aged 28 Days to 36 Months Infected with Respiratory Syncytial Virus”.
2. Clinical Trial Protocol 64041575RSV2002, “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”.