1.0   Title Page

Statistical Analysis Plan

Study M15-539

A Prospective, International, Multicenter, Open-Label, Non-Controlled Study of Safety and Effectiveness of Palivizumab, in Children at High Risk of Severe Respiratory Syncytial Virus (RSV) Infection in the Russian Federation and the Republic of Belarus

Date: 30 January 2017

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3.0   Introduction

This analysis plan reflects Study Protocol M15-539 dated 21 January 2016, including Amendment 1 dated 25 May 2016. It takes into account the ICH Guidelines E3 and E9.

The SAP will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the database lock.

All data will be verified and validated according to the latest version of the integrated data review plan (IDRP).

The analysis will be performed by AbbVie using SAS® in a UNIX environment, the release currently implemented at the time of analysis.

4.0   Study Objectives, Design and Procedures

4.1   Objectives

The objectives of this study are to collect further data on safety and effectiveness of the liquid formulation of palivizumab (Synagis®) administered as monthly intramuscular injections among preterm infants, infants with chronic lung disease (CLD) of prematurity and infants with hemodynamically significant congenital heart disease (CHD) in the Russian Federation and the Republic of Belarus.

4.2   Study Design

This is a Phase 3b, prospective, multicenter, open-label, non-controlled study of immunoprophylaxis with the intramuscular (IM) administration of palivizumab for the prevention of RSV hospitalizations in infants at high risk. Approximately 50 infants will be enrolled in the study and will receive palivizumab solution for injection at 15 mg/kg by IM injection every 30 days for a minimum of 3 and a maximum of 5 injections given during anticipated periods of RSV risk in the community; the number of doses will depend on the time of enrollment during the RSV season. Prior to each injection of study

drug all enrolled subjects will undergo safety assessment. All subjects that received at least one injection of palivizumab will be followed by a telephone contact at 30 and 100 days after their last injection.

All cardiac/respiratory hospitalizations or deterioration in the cardiac/respiratory status in a hospitalized infant will be evaluated by testing nasopharyngeal specimens with a commercially available licensed RSV diagnostic test (RT-PCR) to determine if RSV contributed to the hospitalization or deterioration.

4.3 Sample Size

No formal sample size calculation was performed for this descriptive study and the sample size is based primarily on practical considerations. It is anticipated that approximately 50 subjects will be enrolled. With a sample size of 50 subjects, the width of the 95% exact confidence interval in case of 0, 1, 2, 3 RSV hospitalizations (i.e., event rates of 0%, 2%, 4%, 6%) would be 7.1% (lower bound 0%; upper bound 7.1%), 10.6% (0.1%; 10.6%), 13.2% (0.5%; 13.7%), 15.3% (1.2%; 16.5%), respectively.

4.4 Interim Analysis

No interim analysis will be done.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

All analyses will be performed on the intent-to-treat (ITT) set, defined as all enrolled subjects who received at least one dose of study drug, unless otherwise indicated.

The safety analyses will be performed on the safety set which is identical to the ITT set.

5.2 Variables Used for Stratification of Randomization

Not applicable.

6.0   Analysis Conventions

Definition of Baseline

For any variable, the baseline value is defined as the last non-missing value on or before the date and time (if applicable) of first administration of study drug.

Definition of Analysis Windows

The following visit windows will be used to assign visit numbers for analysis. If the assigned visit number results in more than one non-missing assessment in a given visit window, then the assessment performed closest to the nominal day will be used in analyses. When more than 1 day is of equal proximity to the nominal day, then the data collected after the nominal day will be used in analyses.

Visit windows depend on when a variable is measured during the study.

RxDAY is defined as the number of days between the day of the first dose of study drug and the day of the time point of interest.

RxDAY = date of visit – date of first study drug + 1.

RxDAYs are negative values when the time point of interest is prior to the first study drug dose day. RxDAYs are positive values when the time point of interest is on or after the first study drug dose day. The day of the first dose of study drug is defined as RxDAY 1, while the day prior to the first study drug dose is defined as RxDAY −1 (there is no RxDAY 0).

Table 1. **Visit Windows**

Scheduled Visit Day	Nominal RxDAY	First RxDAY	Last RxDAY
0	1		1
30	30	2	45
60	60	46	75
90	90	76	105
120	120	106	

Vital signs (blood pressure, respiration rate, heart rate, body temperature), body weight and body height values obtained more than 30 days after the last dose of study drug will not be included in the analyses.

Enrollment date is defined as date of first visit.

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

Demographics, baseline characteristics, medical history and previous/concomitant medication will be assessed for the ITT set.

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized.

Continuous data will be summarized with the number of non-missing observations by mean, standard deviation, median, first and third quartile, minimum and maximum values.

Categorical data will be summarized using frequencies and percentages. The number of subjects with missing information will also be summarized; however, percentages will be calculated based on non-missing values.

Tables for subject demographics including body height and weight will also be stratified by sex.

Subject Demographics

- Sex [male, female]
- Age [months] defined as the number of months from date of birth to date of first study drug, i.e., the integer of (age in days/30).
- Age categories [0 – 3, 4 – 6, 7 – 9, 10 – 12, 13 – 15, 16 – 18, 19 – 21, 22 – 24 months)
- Ethnicity [Hispanic or Latino, Not Hispanic or Latino]
- Race [White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multi Race; if Asian: Japanese, Chinese, Korean, Taiwanese, other]
- Body height [cm]
- Body weight [kg]
- Body weight categories [≤ 3.33 kg, > 3.33 to ≤ 6.66 kg, subtotal ≤ 6.66 kg, > 6.66 to ≤ 10.00 kg, > 10.00 to ≤ 13.33 kg, subtotal > 6.66 to ≤ 13.33 kg, > 13.33 kg]

Criteria of High Risk of Severe RSV Infection

- Infant born < 35 weeks gestational age AND ≤ 6 months of age at enrollment
- Infant ≤ 24 months of age at enrollment AND with a diagnosis of Bronchopulmonary Dysplasia (BPD)
- Infant ≤ 24 months of age at enrollment with Hemodynamically Significant Congenital Heart Disease (CHD)
- Any combinations of the above
- *For subjects with CHD:* Subject status [unoperated, partially corrected]
- *For subjects with CHD:* Type of CHD [Cyanotic, Acyanotic with pulmonary hypertension, Acyanotic with daily medication]

Subject's Medical History at Birth/RSV Hospitalization After Birth

- Weeks gestational age (wGA) [weeks]
- Weeks gestational age categories [< 29, 29 – 32, 33 – 35, > 35 wGA]

- Birth weight [grams]
- Subject product of multifetal pregnancy [yes, no]
- Subject hospitalized for RSV after birth [yes, no]
- *If yes:* number of RSV hospitalizations *(categorical)*

Subject's Social History

- Number of rooms in the home *(continuous, categorical)*
- Number of people in the home > 13 years old *(continuous, categorical)*
- Number of other children in the home ≤ 13 years old *(continuous, categorical)*
- subject attends day care [yes, no]
- other children (≤ 13 years old) in the home attend daycare/school [yes, no]
- Number of furred pets inside the home *(continuous, categorical)*
- subject exposed to tobacco smoke in the home [yes, no]

Subject's Alimentary Diet

- subject ever breastfed [yes, no]
- *if ever breastfed:* currently breastfed [yes, no]
- *if ever breastfed:* duration breastfed [months] *(continuous, categorical)*
- *if ever breastfed:* currently receiving non-human breast milk [yes, no]
- *if ever breastfed:* age when non-human breast milk was introduced [months] *(continuous, categorical)*
- *if ever breastfed:* currently receiving solid food [yes, no]
- *if ever breastfed:* age at first solid food intake [yes, no] *(continuous, categorical)*

Mother's Medical History

- Number of pregnancies *(continuous, categorical)*
- Number of deliveries *(continuous, categorical)*
- Number of abortions *(continuous, categorical)*

- Number of miscarriages *(continuous, categorical)*
- subject's mother smoked while pregnant with the subject [yes, no]

Family History/Family History of Atopy and Immunodeficiency

- Father's age at enrollment visit calculated as number of years between father's birth date (imputed as 01 JAN of the birth year) and enrollment date [years]
- Mother's age at enrollment visit calculated as number of years between mother's birth date (imputed as 01 JAN of the birth year) and enrollment date [years]
- Father's highest educational level [illiterate, school, high school, college, post graduate, unknown]
- Mother's highest educational level [illiterate, school, high school, college, post graduate, unknown]
- Family members with asthma [yes, no, unknown]
- Family members with allergic bronchitis [yes, no, unknown]
- Family members with allergic rhinitis/rhinosinusitis [yes, no, unknown]
- Family members with immunodeficiency [yes, no, unknown]

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

Medication is coded in WHODrug.

Prior and concomitant medications will be summarized. A prior medication is defined as any medication taken prior to the first dose of study drug. A concomitant medication is defined as any medication that started prior to the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started after the first dose of study drug, but not after the last dose of study drug. The number and percentage of subjects who had taken medications will be summarized by generic drug name for both prior and concomitant medications.

8.0 Patient Disposition

The number of subjects for each of the following categories will be summarized overall and by country and site:

- Subjects enrolled
- Subjects received at least one dose of study drug
- Subjects who prematurely discontinued study drug
- Subjects who completed study drug
- Subjects who prematurely discontinued the study
- Subjects who completed the study
- Subjects enrolled in first month of RSV season (November)
- Subjects enrolled in second month of RSV season (December)
- Subjects enrolled in third month of RSV season (January)

For the ITT set, the number and percentage of subjects who discontinued study drug or who discontinued from the study, respectively, will be summarized by reason (primary or secondary) and by primary reason.

Furthermore, the following information will be summarized for the ITT set:

- Number of patients observed per visit *(also broken down by enrollment month)*
- Protocol deviations (four major ICH deviations)

○ Inclusion/exclusion criteria met [yes, no] based on the inclusion/exclusion module of the CRF

○ Specification of violated inclusion/exclusion criteria based on the inclusion/exclusion module of the CRF

○ Subject developed withdrawal criteria but was not withdrawn [yes, no]

○ Subject received wrong treatment or incorrect dose [yes, no]

○ Subject received excluded concomitant treatment during the treatment with palivizumab [yes, no]

9.0   Study Drug Exposure and Compliance

Exposure and compliance will be analyzed for the safety set (which is identical to the ITT set).

Exposure

● Number of doses administered *(continuous and categorical, also broken down by enrollment month; subjects who received an extra dose of study drug due to cardiac surgery are shown separately in this breakdown)*

● Total volume injected [ml] *(per visit and total during study, also broken down by enrollment month; subjects who received an extra dose of study drug due to cardiac surgery are shown separately in this breakdown)*

● Total dose of palivizumab [mg] *(per visit and total during study)* calculated as volume injected [ml] * 100 [mg/ml] *(also broken down by enrollment month; subjects who received an extra dose of study drug due to cardiac surgery are shown separately in this breakdown)*

● Duration of exposure [days] calculated as the time from first injection to last injection of study drug + 100 days. In addition to the analysis as continuous endpoint, duration of exposure will be analyzed in the following exclusive duration intervals: 101 – 130, 131 – 160, 161 – 190, 191 – 220, > 220 days. *(also broken down by enrollment month; subjects who received an extra dose of study drug due to cardiac surgery are shown separately in this breakdown)*

Compliance

- Compliance with study drug [%] calculated as (number of injections received/number of injections planned) * 100. *(also broken down by enrollment month; subjects who received an extra dose of study drug due to cardiac surgery are shown separately in this breakdown)* The number of doses planned is calculated based on the month of enrollment and whether the subject completed the study or early discontinued.

- For each visit, the actual number of days between the first dose of study drug and the injection date at that visit will be calculated.

10.0 Effectiveness Analysis

10.1 General Considerations

Analysis Set Used for Effectiveness Analyses

The ITT set will be used for the effectiveness analysis.

Descriptive Analyses

The primary and all secondary effectiveness variables will be described by statistical characteristics. Categorical data will be described by frequency and percentage, quantitative data by mean, standard deviation, minimum, first quartile, median, third quartile and maximum. Also the number of non-missing values will be given.

All analyses including the confidence intervals calculated will be of a descriptive sense.

No imputation of missing values will be done, data will be reported as observed.

10.2 Primary Effectiveness Analysis

RSV hospitalization is the primary effectiveness variable in this study. The following definitions will be applied:

Respiratory and Cardiac Hospitalizations

A respiratory/cardiac hospitalization is defined as a hospital admission for the primary reason to evaluate or treat a respiratory/cardiac condition occurring after the first dose of palivizumab injection through 30 days after the last dose of palivizumab injection. New onset of respiratory/cardiac symptoms in an already hospitalized child, with an objective measure of worsening respiratory/cardiac status will also be considered as a cardiac/respiratory hospitalization.

RSV Hospitalizations

An RSV hospitalization is defined as either 1) a respiratory/cardiac hospitalization with a positive RSV test, 2) new onset of respiratory/cardiac symptoms in an already hospitalized child, with an objective measure of worsening respiratory/cardiac status and a positive RSV test, or 3) death, which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence). To be considered a valid RSV test, the respiratory secretions for the RSV detection must have been collected within 2 days of admission or of worsening of respiratory/cardiac symptoms, respectively.

A hospital admission or a new onset of nosocomial respiratory/cardiac symptoms without an RSV test result will not be counted as RSV-hospitalization in the primary analysis.

Only RSV-associated hospital admissions, new onset of nosocomial respiratory/cardiac symptoms with a positive RSV test, and RSV-associated deaths occurring from the first dose of study drug injection to within 30 days of the last study drug dose will be included in the analyses for the primary endpoint.

The primary analysis will be the calculation of the number and proportion of subjects with RSV hospitalization along with the two-sided 95% exact confidence interval according to Clopper Pearson for the proportion.

In addition, a cross tabulation of reason for hospitalization or type of illness for already hospitalized subjects with new onsets of nosocomial respiratory/cardiac symptoms

[cardiac, respiratory, both] versus result of RSV text [positive, negative, not performed] will be done.

10.3 Secondary Effectiveness Analyses

The following secondary effectiveness variables will be summarized descriptively for all subjects with RSV hospitalization (including new onset of nosocomial respiratory/cardiac symptoms):

- Total number of RSV-hospitalization days;
- Use of increased supplemental oxygen (defined as a new requirement or an increase in supplemental oxygen from prior to the onset of cardiac/respiratory symptoms);
- Total RSV-hospitalization days with increased supplemental oxygen requirement;
- Number of ICU admissions during RSV-hospitalization;
- Total days of RSV-ICU stay;
- Use of mechanical ventilation;
- Total days of mechanical ventilation during RSV-hospitalization.

In case of only one RSV hospitalization in the study, a listing of the above information instead of descriptive summary information will be provided.

Only data corresponding to RSV hospitalization admissions and new onset of nosocomial respiratory/cardiac symptoms that occur within 30 days after the last study drug dose will be included in the analyses.

10.4 Other Effectiveness Analyses

Not applicable.

10.5 Handling of Multiplicity

Not applicable since this is an open-label non-comparative study.

10.6   Effectiveness Subgroup Analysis

Not applicable.

11.0   Safety Analysis

11.1   General Considerations

All safety analyses will be done for the safety set.

All variables will be described by statistical characteristics. Categorical data will be
described by frequency and percentage, quantitative data by mean, standard deviation,
minimum, median and maximum. Also the number of non-missing values will be given.

11.2   Analysis of Adverse Events

11.2.1   Treatment-Emergent Adverse Events

Definition for Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized for two time spans.
TEAEs are defined as any event with an onset date that is after the first dose of study drug
and with an onset date no more than 30 or 100 days, respectively, after the last dose of
study drug. All of the below analyses will be provided for both, the 30-day and the
100-day definition for TEAEs. Events where the onset date is the same as the study drug
start date are assumed to be treatment-emergent. If an incomplete onset date was
collected for an adverse event, the event will be assumed to be treatment-emergent unless
there is other evidence that confirms that the event was not treatment-emergent (e.g., the
event end date was prior to the study drug start date).

Terms to be Summarized

TEAEs will be summarized and presented using primary MedDRA system organ classes
(SOCs) and preferred terms (PTs) according to the most current implemented MedDRA
version. The system organ classes will be presented in alphabetical order and the
preferred terms will be presented in alphabetical order within each system organ class.

Summary Tables

1. Adverse Event Overview

   The number and percentage of subjects experiencing TEAEs will be summarized for the following adverse event categories.

   ● Any TEAE
   ● Any TEAE that was rated by the investigator to have a "reasonable possibility" for a relationship to study drug.
   ● Any treatment-emergent severe adverse event.
   ● Any treatment-emergent serious adverse event.
   ● Any TEAE leading to discontinuation of study drug.
   ● Any TEAE leading to death.

2. Adverse Events by System Organ Class and Preferred Term

   The number and percentage of subjects experiencing TEAEs will be tabulated according to the primary MedDRA system organ class (SOC) and MedDRA preferred term for each treatment group. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total. In addition, the number and percentage of adverse events rated by the investigator as having a relationship to study drug with a "reasonable possibility" will be summarized using the same conventions described above.

   A listing of subject numbers associated with AEs by SOC and PT will be provided.

3. Adverse Events by Maximum Severity

   Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the

same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

4. Adverse Events by Maximum Relationship

Adverse events will also be summarized by maximum relationship to study drug, as assessed by the Investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

Listings of Non-Treatment-Emergent Adverse Events

Pre-treatment adverse events, i.e., adverse events with a start date between informed consent and first study drug treatment will be listed separately and not included in the listings and summary tables of treatment-emergent adverse events.

Adverse events that start more than 100 days after discontinuation of study drug treatment, if reported, will also be listed separately and not included in the listings and summary tables of treatment-emergent adverse events.

11.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

The number and percent of subjects experiencing SAEs (including deaths) and adverse events leading to discontinuation of study drug will be tabulated according to the primary MedDRA system organ class (SOC) and MedDRA preferred term.

In addition to these summary tables, SAEs and AEs leading to discontinuation will be listed.

11.3   Analysis of Laboratory Data

Not applicable.

11.4   Analysis of Vital Signs and Weight

11.4.1   General Considerations

The following vital signs parameters will be assessed prior to and 30 minutes post study drug administration, weight is only measured prior to study drug administration:

- Systolic blood pressure [mmHg]
- Diastolic blood pressure [mmHg]
- Pulse [beats per minute]
- Respiratory rate [breaths per minute]
- Temperature [°C]
- Weight [kg]

Vital signs or weight values obtained more than 30 days after the last dose of study drug will not be included in the analyses.

11.4.2   Statistical Methods

Mean changes from baseline to the different study visits (separately for pre- and post-dose measurements, respectively) will be summarized with the baseline mean, change from baseline mean, standard deviation, and median. Changes from baseline will be tested descriptively using a paired t-test. For analyses of changes from baseline, only those subjects with values both at baseline and at the respective visit will be included.

For each vital sign variable, change from pre-injection value to post-injection value at each visit will also be summarized. Analyses will be performed as described above for the analyses of the change from baseline to each visit.

In case of any extra doses of study drug given due to cardiac surgery, the associated vital signs measurements will be displayed separately.

11.5   Analysis of ECG Parameters

Not applicable.

11.6   Safety Subgroup Analysis (If Applicable)

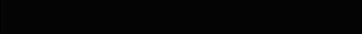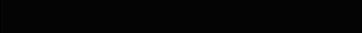Not applicable.

Document Approval

Study M15539 - Statistical Analysis Plan Version 1 - 30Jan2017 (E3 16.1.9)

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Signed by:	Date:	Meaning Of Signature:
████████████	31-Jan-2017 07:49:00 AM	Approver
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