1.0 Title Page

Clinical Study Protocol 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

Incorporating Amendment 1

AbbVie Investigational Product:	Palivizumab
Date:	25 May 2016
Development Phase:	3b
Study Design:	Multicenter, Open-label Study
EudraCT Number:	2016-000221-39
Sponsor:	AbbVie Inc.*
Sponsor/Emergency Contact:	[redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	21. January 2016

The purpose of this amendment is to:

- Update the study objective

  Rationale: *Considering the non-comparative design of the study and the already available data on Synagis® (Palivizumab), the wording for the study objective is modified.*

An itemized list of all changes made in this protocol amendment can be found in Appendix D.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-539
Name of Study Drug: ABT-315/palivizumab/ MEDI-493	**Phase of Development:** 3b
Name of Active Ingredient: ABT-315/palivizumab	**Date of Protocol Synopsis:** 25 May 2016
Protocol Title: 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	
Objective: 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. The lyophilized formulation of palivizumab is currently approved.	
Investigators: Multi-center	
Study Sites: Approximately 20 sites	
Study Population: Male or female children born at ≤ 35 weeks gestational age and ≤ 6 months of age at enrollment, or infants ≤ 24 months of age with a diagnosis of CLD of prematurity requiring on-going medical treatment within the previous 6 months or infants ≤ 24 months of age with hemodynamically significant CHD.	
Number of Subjects to be Enrolled: Approximately 50 subjects will be enrolled into the study.	
Methodology: 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. Children who undergo cardiac surgery with cardiopulmonary bypass through Study Day 150 should receive an additional replacement injection of study drug immediately following the surgery when determined by the physician to be medically stable for an intramuscular (IM) injection. 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. Enrollment will start in November 2016.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Infants at high risk of severe RSV infection defined as fulfilling at least one of the following:
   - Infants born ≤ 35 weeks gestational age AND are ≤ 6 months of age at enrollment;
   - Infants ≤ 24 months of age at enrollment AND with a diagnosis of BPD (defined as oxygen requirement at a corrected gestational age of 36 weeks) requiring intervention/management (i.e., oxygen, diuretics, bronchodilators, corticosteroids, etc.) anytime within 6 months prior to enrollment;
   - Infants ≤ 24 months of age at enrollment with hemodynamically significant CHD, either cyanotic or acyanotic, unoperated or partially corrected. Children with acyanotic cardiac lesions must have pulmonary hypertension (≥ 40 mmHg measured pressure in the pulmonary artery [ultrasound acceptable]) or the need for daily medication to manage CHD. Infants with following conditions are not eligible: hemodynamically insignificant small atrial or ventricular septal defects, patent ductus arteriosus, children with aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone.
2. Informed Consent Form signed by parent(s)/legal guardian(s).

Main Exclusion:

1. Hospitalization at the time of enrollment (unless discharge is anticipated within 14 days).
2. Mechanical ventilation (including continuous positive airway pressure, CPAP) at the time of enrollment.
3. Life expectancy < 6 months.
4. Unstable cardiac or respiratory status, including cardiac defects so severe that survival is not expected or for which cardiac transplantation is planned or anticipated.
5. Active respiratory illness, or other acute infection.
6. Known renal impairment (e.g., ≥ 25% decrease in age appropriate creatinine clearance), as determined by the Investigator.
7. Known hepatic impairment (e.g., albumin < 2.0 g/dL), as determined by the Investigator.
8. Unstable neurological disorder (includes, but is not restricted to epilepsy and, decompensated hydrocephaly).
9. Known immunodeficiency, including Human Immunodeficiency Virus (HIV) infection as determined by the Investigator
10. Mother with known HIV infection unless the child has been proven to be not infected with HIV
11. Allergy to immunoglobulin products
12. Prior receipt of RSV vaccine or prophylaxis (e.g., palivizumab); or administration of a product possibly containing RSV-neutralizing antibody or any other polyclonal antibody within 100 days prior to enrollment (includes, but is not restricted to, the following: RSV hyperimmunoglobulin, polyclonal intravenous immunoglobulin, cytomegalovirus hyperimmunoglobulin, varicella zoster hyperimmunoglobulin).
13. Previous enrollment in this trial.
14. Subject is currently participating in another investigational study (drug or device) or has participated in an investigational drug study (i.e., receiving or has received investigational product) within 1 month or 5 times the investigational drug half-life, whichever is longer, prior to enrollment.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 15. For any reason, subject is considered by the investigator to be an unsuitable candidate for this study.	
Investigational Product:	Palivizumab in sterile vials containing 100 mg of palivizumab in 1 mL of a sterile preservative-free solution for injection product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine
Dose:	Palivizumab 15 mg/kg every 30 days
Mode of Administration:	Intramuscular injection
Duration of Treatment: All subjects will receive at least 3 and a maximum of 5 monthly doses of palivizumab during the 2016 – 2017 RSV season.	
Criteria for Evaluation: **Effectiveness:** RSV hospitalization is the primary effectiveness variable in this study, occurring from the 1st dose through 30 days after the last injection of palivizumab • 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) deaths, which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence defined as a positive RSV test). For each hospitalization the reason for admission and accompanying respiratory and/or cardiac signs and symptoms will be recorded. **Secondary Variables** • 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. **Safety:** Safety evaluations include adverse event monitoring and collection, physical examinations, and vital sign measurements as a measure of safety and tolerability during the study and/or follow-up period. Concomitant medications will also be collected to aid the safety assessment.	
Statistical Methods: **Effectiveness:** The primary analysis will be the calculation of the number and proportion of subjects with RSV hospitalization along with the 95% exact confidence interval for the proportion. Data will be summarized descriptively. For continuous variables, the mean, standard deviation, median, minimum and maximum values will be calculated. For categorical variables, the number and percentage of subjects in each category will be calculated for non-missing data.	

Statistical Methods (Continued):

Safety:

Safety and tolerability of palivizumab will be assessed by summarizing adverse events occurring from first dose through follow-up contact at 100 days following the last injection of study drug. In addition, vital signs recorded at each safety evaluation will be assessed by presenting changes and percent changes from baseline to each safety assessment.

Sample Size:

The objective of this study is to collect further data on the effectiveness and safety of the liquid formulation of palivizumab in young children at high risk of severe RSV disease in the Russian Federation and the Republic of Belarus. Thus, the sample size was selected to meet this objective and is not primarily based on statistical considerations. However, 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.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
CA	Community acquired
CHD	Congenital heart disease
CLD	Chronic lung disease
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRF	Case report form
EDC	Electronic Data Capture
ET	Early Termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart rate
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional review board
IRT	Interactive Response Technology
LEC	Local Ethics Committee
LPV	Last prophylaxis visit
LRTI	Lower respiratory tract infection
RR	Respiratory rate
RSV	Respiratory syncytial virus
SAE	Serious adverse event
T°C	Temperature in degrees Celsius
wGA	Weeks, gestational age

WHO	World Health Organization

Definition of Terms

Preterm infants	For the purposes of this trial, only preterm infants born ≤ 35 weeks gestational age are eligible.
BPD	Clinical diagnosis is defined as oxygen requirement at a corrected gestational age of 36 weeks.
Liquid formulation	Solution for Injection formulation of palivizumab
Gestational age	Time in completed weeks from mother's last menstrual period until birth.
Corrected gestational age	Time from mother's last menstrual period until birth plus weeks after birth.
RSV-hospitalization	The primary endpoint of this study. A hospitalization with a positive RSV test as defined in Section 8.1.3.
Follow-up Period	Time up to 100 days from last study drug injection.

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3.0 Introduction

Respiratory syncytial virus (RSV) causes respiratory tract illnesses in both children and adults,[1-4] and is the major cause of lower respiratory tract infections (LRTIs) in infants. RSV is a ubiquitous pathogen responsible for epidemics of disease globally.[5] The seasonality of RSV infection varies regionally. In temperate regions disease occurs mostly in the cold season (i.e., October through March in the Northern hemisphere).[6] Prevalence of RSV in infants hospitalized with lower respiratory tract infection (LRTI) in developed countries varies from 18% – 33%.[7-9] In a sample of children aged ≤ 2 years who were hospitalized for LRTI during the RSV season in the Russian Federation, 38% tested positive for RSV.[10]

In infants and young children, RSV disease may present with upper and/or lower respiratory tract signs and symptoms which could include fever, runny nose, cough, wheezing, lung hyper-expansion, and hypoxia.[11,12] In healthy infants and young children, where the disease is limited to the upper respiratory tract, symptoms are usually mild and resolve spontaneously within 4 to 7 days of onset.

Infants and children born prematurely, have a diagnosis of BPD (also known as CLD of prematurity), or those with congenital heart disease (CHD) are particularly vulnerable to RSV infection.[7] RSV is more likely to progress to the lower respiratory tract and cause more serious disease in these high-risk children. In prospective studies conducted over a 16-year period, it was found that 60% of children with underlying high-risk conditions were hospitalized for RSV lower respiratory tract disease. These underlying conditions included prematurity (less than 36 weeks' gestation), cardiac disease, chronic lung disease, immunodeficiencies and multiple congenital abnormalities.[13] Furthermore, the course of illness tends to be more severe in these children, and is associated with higher rates of hospitalization, intensive care unit admission, mechanical ventilation, and death.[3,4,8,9,14]

Palivizumab (ABT-315, also referred to as MEDI-493, trade name Synagis®) is a humanized IgG1 monoclonal antibody directed to an epitope in the A antigenic site of the F (fusion) protein of RSV. The palivizumab antibody is composed of human (95%) and

murine (5%) amino acid sequences. Palivizumab has potent neutralizing and fusion-inhibitory activity against RSV subtype A and B strains. Palivizumab serum concentrations of approximately 30 μg/mL have been shown to produce a 99% reduction in pulmonary RSV replication in the cotton rat model.

In a global, randomized, placebo-controlled trial of RSV disease prophylaxis (MI-CP018, IMpact-RSV trial), 1502 high-risk children received 5 monthly doses of 15 mg/kg palivizumab (1002 subjects) or placebo (500).[15] Children enrolled in the trial included 1) infants born ≤ 35 wGA and ≤ 6 months of age at the onset of RSV season; 2) infants ≤ 24 months of age and with a diagnosis of BPD who received intervention/management (i.e., oxygen, diuretics, bronchodilators, corticosteroids) within 6 months of enrollment. Palivizumab treated children exhibited a reduction in the incidence of RSV related hospitalization by 55% compared to placebo (10.6% in the placebo group versus 4.8% in palivizumab group, $p < 0.001$). In the MI-CP018 trial, anti-palivizumab antibody immunogenicity following palivizumab injection was low and comparable to the placebo arm.[15]

In a second global, randomized, placebo-controlled trial of RSV disease prophylaxis (MI-CP048) in 1287 subjects ≤ 24 months of age with hemodynamically significant CHD (639 palivizumab; 648 placebo), 5 monthly doses of 15 mg/kg palivizumab reduced the incidence of RSV hospitalization by 45% (9.7% in the placebo group and 5.3% in the palivizumab group, $p = 0.003$), as well as total days of RSV hospitalization (56% reduction, $p = 0.003$) and total RSV hospitalization days with increased supplemental oxygen (73% reduction, $p = 0.014$).[16]

Adverse drug reactions (ADRs) reported in the prophylactic pediatric studies were similar between the placebo and palivizumab treated groups. The majority of ADRs were transient and mild-to-moderate in severity.

A prospective, multicenter, open-label, non-comparative clinical study (Study W10-664) conducted in the Russian Federation evaluated immunoprophylaxis with palivizumab for the prevention of severe lower respiratory tract RSV infection in infants at high risk

including preterm infants, infants with BPD and infants with CHD. A total of 100 infants received palivizumab IM 15 mg/kg for passive immune protection during the RSV season. No cases of RSV hospitalization were reported during the study period.[17] Twelve treatment-emergent serious adverse events occurred in 10 subjects in Study W10-664. Most of the serious adverse events were categorized as infectious diseases such as bronchitis, enteritis, tonsillitis, or pneumonia. All events were assessed as not related to study drug. One nonserious treatment-emergent adverse event of atopic dermatitis led to discontinuation of the study drug. This event was assessed as mild in severity and possibly related to study drug. No clinically relevant changes in vital signs were observed during the study. In this study palivizumab was found to be safe and well tolerated in this mixed population of subjects at risk for serious RSV infection in the Russian Federation.

Palivizumab is approved for once a month intramuscular (IM) injection at a dose of 15 mg/kg of body weight during the RSV season. The formulation currently approved in the Russian Federation and the Republic of Belarus is the lyophilised formulation, presented as 50 mg and 100 mg vial strengths. The solution for injection formulation of palivizumab requires no reconstitution and is approved in more than 40 countries for the same indication and patient populations as the lyophilised formulation. Both the lyophilised and solution for injection formulations of palivizumab have been shown to be bioequivalent and to have similar safety profiles.

This international, multicenter, open-label study is intended to collect further data on the safety and effectiveness of palivizumab solution for injection in children at high risk of severe respiratory syncytial virus infection in the Russian Federation and the Republic of Belarus.

Additional information on palivizumab can be found in the Investigator's Brochure.

3.1 Differences Statement

Synagis® (Palivizumab) is indicated for the prevention of serious LRTI caused by RSV in children at high risk of RSV disease. Palivizumab solution for injection was studied in two studies as the control group for an Investigational drug which included subjects in the Russian Federation. This study will collect further data on safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population.

3.2 Benefits and Risks

The present study is a prospective, multicenter, open-label, non-controlled study to collect further data on safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population of preterm infants, infants with chronic lung disease (CLD) of prematurity and infants with hemodynamically significant congenital heart disease (CHD). Palivizumab is the only product currently approved for prophylaxis of serious disease caused by respiratory syncytial virus (RSV) infection for the indicated high-risk paediatric populations. The efficacy of palivizumab (both lyophilized and solution for injection formulation) has been demonstrated in clinical trials in the indicated high-risk populations of preterm infants ≤ 6 months of age, and young children ≤ 2 years of age with bronchopulmonary dysplasia (BPD) or hemodynamically significant congenital heart disease (HSCHD). The safety profile of palivizumab has been well established in both clinical trials and more than 15 years of marketed use. The benefit-risk ratio is favorable for palivizumab used in the indicated patient populations.

4.0 Study Objective

The objective of this study is to collect further data on safety and effectiveness of palivizumab solution for injection administered as monthly intramuscular injections among preterm infants (≤ 35 wGA), infants with CLD of prematurity and infants with hemodynamically significant CHD in the Russian Federation and the Republic of Belarus.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3b, prospective, multicenter, open-label, non-controlled clinical study of immunoprophylaxis with Synagis® (Palivizumab) solution for injection for the prevention of severe lower respiratory tract RSV infection in infants at high-risk.

Approximately 50 subjects will be enrolled into the study in approximately 20 study sites in the Russian Federation and the Republic of Belarus. The target enrollment number for each of the subpopulations of CHD, BPD and pre-terms is a minimum of approximately 5 subjects.

Enrollment will start in November 2016 and will continue to no later than January 2017. All enrolled subjects will receive 15 mg/kg Synagis® (Palivizumab) solution by intramuscular (IM) injection every 30 days for a minimum of 3 and a maximum of 5 injections during the RSV season defined as November 2016 through March 2017. Children who undergo cardiac surgery with cardiopulmonary bypass through Study Day 150 should receive an additional replacement injection of study drug immediately following the surgery when determined by the physician to be medically stable for an intramuscular (IM) injection. Any subsequent doses of study drug will continue to be given according to the protocol-specified dosing schedule as described in Section 5.5. Each injection of palivizumab will occur at the study site and prior to each injection subjects will undergo safety assessments. Follow-up telephone calls with parent(s)/legal guardian(s) of all subjects that received at least one palivizumab injection will occur 30 and 100 days after their last injection of palivizumab.

All cardiac/respiratory hospitalizations or deterioration in the cardiac/respiratory status in a hospitalized infant will be evaluated by testing respiratory secretions using a validated real-time RT-PCR RSV diagnostic test to determine if RSV contributed to the hospitalization or deterioration.

The study was designed to enroll approximately 50 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled in the study.

5.2 Selection of Study Population

Infants at high risk of severe RSV infection (including preterm infants, infants with BPD and infants with hemodynamically significant CHD) will be identified as candidates for the study on the basis of routine assessments, and the parent(s)/legal guardians will be asked to provide consent by reading and signing an Informed Consent Form.

Once the Informed Consent is signed by parent(s)/legal guardian(s), the study Inclusion/Exclusion Criteria will be checked. Infants who meet all of the Inclusion and none of the Exclusion Criteria will be assigned with a Subject Number and enrolled into the study.

5.2.1 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled into the study.

1. Infants at high risk of severe RSV infection defined as fulfilling at least one of the following:
    - Infants born ≤ 35 w GA AND are ≤ 6 months of age at enrollment;
    - Infants ≤ 24 months of age at enrollment AND with a diagnosis of BPD (defined as oxygen requirement at a corrected gestational age of 36 weeks) requiring intervention/management (i.e., oxygen, diuretics, bronchodilators, corticosteroids, etc.) anytime within 6 months prior to enrollment;
    - Infants ≤ 24 months of age at enrollment with hemodynamically significant CHD, either cyanotic or acyanotic, unoperated or partially corrected. Children with acyanotic cardiac lesions must have pulmonary hypertension (≥ 40 mmHg measured pressure in the pulmonary artery [ultrasound acceptable]) or the need for daily medication to manage CHD. Infants with following conditions are not eligible: hemodynamically insignificant small

atrial or ventricular septal defects, patent ductus arteriosus, children with aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone.

2. ICF signed by parent(s)/legal guardian(s).

Rationale for Inclusion Criteria

1 To select the appropriate subject population

2 In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Hospitalization at the time of enrollment (unless discharge is anticipated within 14 days).
2. Mechanical ventilation (including continuous positive airway pressure, CPAP) at the time of enrollment.
3. Life expectancy < 6 months.
4. Unstable cardiac or respiratory status, including cardiac defects so severe that survival is not expected or for which cardiac transplantation is planned or anticipated.
5. Active respiratory illness or other acute infection.
6. Known renal impairment (e.g., ≥ 25% decrease in age appropriate creatinine clearance), as determined by the Investigator.
7. Known hepatic impairment (e.g., albumin < 2.0 g/dL), as determined by the Investigator.
8. Unstable neurological disorder (includes, but is not restricted to epilepsy and, decompensated hydrocephaly).
9. Known immunodeficiency, including Human Immunodeficiency Virus (HIV) infection as determined by the Investigator.

10. Mother with known HIV infection unless the child has been proven to be not infected with HIV.
11. Allergy to immunoglobulin products.
12. Prior receipt of RSV vaccine or prophylaxis (e.g., palivizumab); or administration of a product possibly containing RSV-neutralizing antibody or any other polyclonal antibody within 100 days prior to enrollment (includes, but is not restricted to, the following: RSV hyperimmunoglobulin, polyclonal intravenous immunoglobulin, cytomegalovirus hyperimmunoglobulin, varicella zoster hyperimmunoglobulin).
13. Previous enrollment in this trial.
14. Subject is currently participating in another investigational study (drug or device) or has participated in an investigational drug study (i.e., receiving or has received investigational product) within 1 month or 5 times the investigational drug half-life, whichever is longer, prior to enrollment.
15. For any reason, subject is considered by the investigator to be an unsuitable candidate for this study.

Rationale for Exclusion Criteria

1 – 11, 15	To ensure safety of the subjects throughout the study
12 – 14	To avoid bias for the evaluation of effectiveness and safety by concomitant or prior use of other medications

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) administered to the subject during 2 weeks prior to enrollment, at the time of enrollment, or received during the study until 100 days after the last study drug injection must be recorded in the primary documentation and the study case report form (CRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose and frequency.

The AbbVie Monitor should be contacted if there are any questions regarding prior or concomitant therapy(ies).

5.2.3.1 Prior Therapy

Any prior receipt of RSV vaccine or prophylaxis (e.g., palivizumab); or administration of a product possibly containing RSV-neutralizing antibody within 100 days prior to enrollment (includes, but is not restricted to, the following: RSV hyperimmunoglobulin, polyclonal intravenous immunoglobulin, cytomegalovirus hyperimmunoglobulin, varicella zoster hyperimmunoglobulin) is not allowed as they may have an effect on RSV infection.

5.2.3.2 Concomitant Therapy

The following medications are not allowed during the study unless medically required:

- Immunoglobulin products possibly containing RSV antibodies such as intravenous immunoglobulins (blood transfusions are permitted);
- Chronic immunosuppressive medication (topical calcineurin inhibitors, topical and inhaled corticosteroids as well as short-course [≤ 7 consecutive days] systemic steroids are permitted);
- Any investigational agents.

Any concomitant treatment administered from first dose up to 100 days after last study drug injection will be documented on the appropriate CRF.

Receipt of any of the above during the study must be immediately (within 1 working day) reported to the sponsor since they may affect RSV infection.

5.3 Effectiveness and Safety Assessments/Variables

5.3.1 Effectiveness and Safety Measurements Assessed and Flow Chart

The number of RSV hospitalizations registered during the study (detailed explanation is in Section 5.3.2.1) will be assessed for effectiveness.

Safety measurements will be based on the safety parameters monitored during the study and collected adverse events.

The following hospitalization data will be collected in the eCRF and recorded in the subject's source:

Upon any admission to hospital, the date, time and reason for admission must be recorded. The amount of supplemental oxygen must be recorded where applicable. In cases of a cardiac/respiratory illness admission, the Investigator/designee must obtain respiratory secretions within 2 days of admission for RSV detection. For cardiac/respiratory hospitalizations, a cardiac evaluation of the subject must be done and any lower respiratory tract illness signs and symptoms present (retractions, rhonchi, wheezing, crackles or rales), must be recorded, including any associated signs and symptoms as coryza, fever, apnea.

If there is evidence of new onset of respiratory/cardiac symptoms in an already hospitalized child, the Investigator/designee must assess the cardiac/respiratory illness of the subject and record any lower respiratory tract illness signs and symptoms present (retractions, rhonchi, wheezing, crackles or rales) including any associated signs and symptoms as coryza, fever, apnea. Any cardiac deterioration as indicated by unplanned or early cardiac surgery, interventional catheterization or extensive additional medical management of the cardiac condition must be recorded. New requirements or an increase in supplemental oxygen from prior to the onset of cardiac/respiratory symptoms or the need for new or additional mechanical ventilation must be also be recorded. In cases where a cardiac/respiratory deterioration is diagnosed in an already hospitalized child, the

Investigator/designee must obtain respiratory secretions for the RSV detection within 48 hours of the new onset of cardiac/respiratory symptoms.

In cases of cardiac/respiratory hospitalization or deteriorations any supplemental oxygen, ICU admissions or mechanical ventilation must be recorded if applicable.

Upon discharge of the subject, the hospital discharge summary completed with date and time of discharge and the diagnosis/diagnoses must be filed in the subject's source. In case of cardiac/respiratory hospitalization, the duration of the hospitalization for cardiac/respiratory illness must be recorded.

The following procedures will be performed during the study and data collected:

- Medical history. Information about all relevant past and current illnesses and conditions will be collected with the special attention to cardiac and pulmonary systems.
- Birth history. Single/multiple gestation, breast-feeding, gestational age and birth weight.
- Demographics: Race, date of birth, and sex.
- Social risk factors. Maternal tobacco smoking during pregnancy, maternal pregnancy history, passive tobacco smoke exposure, number and age of siblings in the household, number of individuals living in the household, number of rooms in the household, daycare attendance, daycare/school attendance of other children, family history of atopy and immunodeficiency, furred pets in the household, age of mother and father, parents' educational level.
- Physical examination and weight. This will include complete physical examination, with the special attention to cardiac and pulmonary systems.
- Body length/height.
- Vital signs (heart rate [HR], blood pressure [BP], respiration rate [RR], and temperature [T°C]). Vital signs will be measured prior to and 30 minutes after administration of the study drug. BP will be measured (using the appropriate

cuff size) 1 time in the supine position. T°C can be measured orally, per axillary or rectally.

- Cardiac/respiratory hospitalization data: Date of admission for cardiac/respiratory illness as well as date of deterioration in the cardiac/respiratory status while hospitalized, and date of death due to RSV will be collected, along with dates of RSV testing and test results.
- RSV-hospitalization data. For RSV-positive hospitalizations the following information will be collected in addition to standard serious adverse event (SAE) data: dates of intensive care unit (ICU) admission and discharge, supplemental oxygen and/or mechanical ventilation start and stop dates and the amount of oxygen.
- Prior and concomitant medication use (Section 5.2.3).
- Adverse event information (Section 6.1.1).
- Family History: Subject's social history and Diet, mother's medical history and the family's social background.

The study activities are presented in Appendix C. Study Activities and the study timelines and visit calendar in Table 1.

5.3.1.1 Study Procedures

The study procedures are outlined in Appendix C and discussed in detail in this section, with the exception of the collection of adverse event information (Section 6.1.4), prior, and concomitant therapy (Section 5.2.3) and subject informed consent (discussed in Section 9.3). Investigators/designees will record all study data in the subject's source documentation and then on the appropriate eCRFs, with the exception of the RSV diagnostic test result which will be provided to the Sponsor electronically from the central laboratory.

All study assessments, including vital signs, must be performed prior to the administration of palivizumab solution for injection. Study drug should be injected as soon as possible following the other study procedures. A second measurement of Vital signs will also be done 30 minutes after administration of the study drug.

Patient Card

The Investigator/designee will provide the parent(s)/legal guardians with the patient card and advise them to carry this card with them throughout the entire study. Parent(s)/legal guardian(s) must provide the card to any non-study physician/hospital in case of an emergency. The patient card provides information on subject participation in the study and the site contact information.

Assignment of Subject Number

For all subjects that fulfill all of the Inclusion- and none of the Exclusion criteria and whose parent(s) or legal guardian(s) have signed the ICF, the investigator/designee will register the subject in the Interactive Response Technology system (IRT) to obtain a Subject Number.

Those numbers will be unique 4-digit numbers and will begin with a 2 digit site number, the next 2 digits will represent the subject number (e.g., 1001). Enrolled subjects will keep their subject number throughout the study.

Medical and Birth History

A complete medical and birth history, including all past and current illnesses and conditions will be collected at Day 1 of the study. The gestational age will be calculated by the Investigator/designee.

Demographics and Social History

At the enrollment visit the Investigator/designee will obtain the social history and demographics by interviewing the parent(s)/legal guardian(s) and record the data in the subject's source and in the eCRF.

Physical Examination and Weight

A complete physical examination will be performed at visits specified in Appendix C. A sympton-directed physical examination may be performed at any other visit, when necessary. Any significant physical examination fndings after the first dose of study drug will be recorded as adverse events.

Body Length/Height

The Investigator/designee will measure body length/height as indicated in the visit schedule in Appendix C and record the information in the subject's source and the eCRF.

Vital Signs

At each of the on-onsite study visits, vital signs will be taken prior to the study drug injection and repeated at 30 minutes after the study drug injection.

Assessment of RSV Hospitalizations

At every subject visit during treatment up to the follow up phone contact 1, the investigator/designee will follow-up on any subject hospitalizations for respiratory and/or cardiac reasons or any onset of new respiratory and/or cardiac symptoms in an already hospitalized subject with the parent(s)/legal guardian(s). The investigator/designee will follow the documentation requirements for RSV hospitalizations and take a note in the subject's source.

In case of cardiac/respiratory hospitalization, an RSV test might be taken by the investigator or designee if the test can be conducted within 48 hours of the hospitalization.

Follow-Up Phone Contact 1

The contact will be performed via telephone. The contact date is calculated as the date of the last prophylaxis visit (LPV) +30 Days (+5 day window is allowed). This telephone

contact will also be performed in all subjects discontinued from the study (unless the reason for discontinuation is withdrawal of consent).

The following procedures will be performed during the telephone call:

1. Record all adverse events (serious and nonserious) in source documents and on the appropriate CRF. Report SAE(s) within 24 hours of becoming aware of the SAE(s).
2. Record all concomitant medications.
3. Collect information about hospitalizations, if applicable.

Follow-Up Phone Contact 2

The contact will be performed via telephone. The contact date is calculated as the date of the last prophylaxis visit (LPV) +100 Days (+5 day window is allowed). This telephone contact will also be performed in all subjects discontinued from the study (unless the reason for discontinuation is withdrawal of consent).

The following procedures will be performed during the telephone call:

1. Record all adverse events (serious and nonserious) in source documents and on the appropriate CRF. Report SAE(s) within 24 hours of becoming aware of the SAE(s).

RSV Diagnostic Test

In case of a respiratory/cardiac hospitalization or prolongation of existing hospitalization associated with respiratory/cardiac symptoms (Section 5.3.2.1), the investigator or designee will obtain a respiratory secretion specimen by nasopharyngeal swab, nasopharyngeal lavage or aspiration for RSV detection. Tracheal secretions may be obtained in cases when a child is intubated. The specimen will be collected as soon as possible, within 48 hours of a respiratory/cardiac hospitalization or new

respiratory/cardiac symptoms in a hospitalized infant. Respiratory secretions in all cases of a respiratory/cardiac hospitalization or prolongation of existing hospitalization associated with respiratory/cardiac symptoms will be collected using nasopharyngeal lavage or aspiration technique (see below for details) as described and tested in a central laboratory for RSV using a validated real-time RT-PCR RSV diagnostic test.

In the event of acute respiratory/cardiac hospitalization at a hospital other than the study site, parent(s)/legal guardian(s) are requested to inform the study site immediately. The Investigator or designee must make arrangements to collect a respiratory secretion specimen for RSV testing as soon as possible, but no later than 48 hours following the admittance of the subject to the non-enrolling hospital. Permission will be sought in the consent form for examination of medical records from all such hospitalizations.

The parent(s)/legal guardian(s) will be instructed that the study site will be the preferred place to obtain a respiratory secretion specimen for RSV detection in the case of hospitalization.

Collection of Nasopharyngeal Specimen for RSV Testing

Specimen collection for RSV diagnostic testing may include either of the following techniques. The goal is to obtain a specimen containing epithelial cells and not simply exudate from the nares:

- Nasopharyngeal Swab Method
- Nasopharyngeal Wash: Syringe Method
- Nasopharyngeal Wash: Bulb Method
- Vacuum-assisted Nasopharyngeal Aspirate Method

Follow the instructions outlined in the central lab manual to obtain a specimen using the site preferred method.

Central Laboratory

A central laboratory will be utilized to process the specimen and provide results for the RSV diagnostic tests. Instructions regarding the processing and shipping of the specimen will be provided by the central laboratory chosen for this study. The certified laboratory chosen for this study is ICON Central Lab. Specimen will be sent to:

ICON Central Laboratories, Inc.
South County Business Park
Leopardstown, Dublin 18
Ireland

ICON Central Laboratories, Inc.
123 Smith Street
Farmingdale, NY 11735
USA

5.3.2 Effectiveness Variables

5.3.2.1 Primary Variable(s)

RSV-hospitalization is the primary effectiveness variable in this study.

Respiratory and Cardiac Hospitalizations

A respiratory/cardiac hospitalization is defined as a hospital admission for the primary reason to evaluate or treat of 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. For each hospitalization, including respiratory/cardiac hospitalizations, the reason for admission and accompanying respiratory and/or cardiac signs and symptoms will be recorded.

RSV hospitalizations will be collected from the 1st dose of palivizumab injection through 30 days after the last dose of palivizumab injection.

5.3.2.2 Secondary Variable(s)

- 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.

5.3.3 Safety Variables

Safety and tolerability of palivizumab will be assessed by summarizing adverse events occurring from first dose of study drug through 30 days following the last injection of study drug. In addition, adverse events occurring from first dose of study drug through 100 days following the last injection of study drug will also be presented. Vital signs and any physical findings on examinations at each visit will be assessed.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced unless it is mutually agreed upon, in writing, by the investigator and AbbVie. Subjects that discontinue from treatment should be followed per protocol and sites should make every attempt to call the subject's parent(s)/legal guardian(s) after 30 and 100 days of the last study drug injection in order to obtain the Follow-up contact 1 and 2 information as outlined in Appendix C.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded and, if feasible, a physical examination, vital signs measurement, an assessment of adverse events, RSV hospitalizations and concomitant medication assessment will be performed as soon as possible after discontinuation from the study.

If a subject is discontinued from the study with an ongoing adverse event the investigator/designee will attempt to provide follow-up until a satisfactory clinical resolution of the adverse event is achieved.

Subjects will be considered as a lost to follow-up if no contact has been established by the time of last subject last visit. The investigator/designee is requested to perform at least three attempts to contact the subject's parent(s)/legal guardian(s). All attempts have to be documented in the subject's source documents.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable

cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

Subjects will receive 15 mg/kg palivizumab administered by IM injection every 30 days for a total of at least 3 doses and a maximum of 5 monthly doses except children who undergo cardiac surgery with cardiopulmonary bypass who will receive 6 doses as described below. Following enrollment into the study and the initial injection of palivizumab at Visit 1, subjects will return to the site for visit assessments and palivizumab injections at Days 30 (–5 days), 60 (±5 days), and if applicable, Days 90 ±5 days) and 120 ±5 days).

The total number of individual palivizumab injections will be determined by the time of enrollment into the study shown in Table 1.

Subjects who develop RSV infection should continue to receive monthly doses of palivizumab throughout the RSV season up to a maximum of 5 palivizumab injections.

Subjects who undergo cardiac surgery with cardiopulmonary bypass during their Prophylaxis Period should receive one additional injection of Synagis® (Palivizumab) IM 15 mg/kg as soon as possible following completion of the surgery. The date and time when the subject is assessed medically stable for an IM injection should be determined by the Investigator/designee. Any subsequent doses of study drug will continue to be given according to the initial protocol-specified monthly dosing schedule.

5.5.1 Treatments Administered

Synagis® (Palivizumab) solution for injection vials (100 mg/mL) will be the study medication for this study. Synagis® (Palivizumab) will be provided as a sterile solution for injection.

Study drug will be administered IM using aseptic technique by the research staff or designee (health care professional) at the study site. The injection should be done preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used as the injection site because of the risk of damage to the sciatic nerve. The subject should be weighed before the injection, and the dose per visit calculated as follows:

The dose per visit (volume in mL)* = subject weight (kg) × 15 mg/kg/100 mg/mL.

* Result will be rounded up to the nearest 0.01 mL. Injection volumes over 1 mL should be given as a divided dose.

5.5.2 Identity of Investigational Product

Synagis® (Palivizumab) is a humanized monoclonal IgG derived from the NSO cell line and is specific for the F protein of RSV. Palivizumab is provided in vials containing 100 mg of palivizumab in 1 mL (100 mg/mL) of a sterile preservative-free solution for injection product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine.

5.5.2.1 Packaging and Labeling

Palivizumab will be supplied as a 1 mL solution for Injection in vials. The study medication will be labelled per the country requirements. The labels must remain affixed to the vials and cartons.

5.5.2.2 Storage and Disposition of Study Drug

Upon receipt and until use, palivizumab must be stored in its original container between 2°C and 8°C Study medication must not be frozen. Storage room or refrigerator will have a temperature recording device that will indicate the high and low temperatures in at least

a 24 hours period, as well as the temperature at the time recorded. Upon receipt of the study drug, the site will acknowledge receipt in the IRT system.

Temperatures outside of the specified storage range should be reported via the IRT system immediately. If the IRT system is not available, a temperature excursion reporting form should be completed in its entirety and faxed to the appropriate fax number as noted on the form along with copies of the up-to-date site accountability log and the appropriate temperature log up to the date of reporting the excursion, so that a determination can be made as to the continued acceptability of the drug. A copy of the completed form will be returned to the study site for retention in the Investigator Site File.

The Investigational product is for investigational use only and is to be used within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the condition specified on the label until used.

5.5.3 Method of Assigning Subjects to Treatment Groups

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

5.5.4 Selection and Timing of Dose for Each Subject

All subjects will receive palivizumab 15 mg/kg IM every 30 days. A ±5-day allowance window is permitted, except for the Visit 2 (Day 30), where only –5-day window is allowed. Subjects will receive at least 3 and a maximum of 5 monthly injections of palivizumab during the 2016 – 2017 RSV season. Palivizumab may be administered at any time during the visit day. All study visit assessments must be performed prior to palivizumab IM injection. Vital signs will be measured before dosing and 30 min after study drug injection. The Investigator/designee will check for any AEs after study drug injection at the visit.

The number of individual doses is determined by the month of enrollment in Table 1.

Table 1. Subject Dosing Timeline

November 2016	December 2016	January 2017	February 2017	March 2017	Total Doses[a]
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	5
	Visit 1	Visit 2	Visit 3	Visit 4	4
		Visit 1	Visit 2	Visit 3	3

a. An extra dose of palivizumab will be administered in the event of a cardiac surgery with cardiopulmonary bypass surgery.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The used vials will be retained by the Investigator or designee after each injection. An exact date of injection will be recorded for each subject. An overall accountability of study drug will be performed and verified by the site and the AbbVie monitor. An explanation will be recorded for any discrepancies.

As long as the study drug is administered solely by the study center personnel, and the subject receives all doses in the defined timelines, the subject will be considered compliant. If any of the applicable doses was missed or administered outside of the allowance window, the subject will be considered non-compliant. Thus, the compliance will only be calculated on the study level (i.e., percentage of subjects, who received all applicable doses within the defined timelines).

5.5.7 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via direct recording in the IRT system. An accurate (running) inventory of study drug will be kept per subject by the site. An overall accountability of the study drug will be performed on an ongoing basis and verified by the AbbVie monitor throughout the treatment period.

Used drug should be destroyed on site, according to local law. All unused study drug unit doses must be inventoried, accounted for, and returned to the destruction depot or destroyed on site, according to local law. All empty study drug units shall be disposed of onsite following completion of study drug accountability and reconciliation procedures. Final drug accountability will be verified by the monitor at the end of study drug treatment at the site.

The site must record misplaced or damaged study drug units in the IRT system. Replacement study drug may only be dispensed to the site by contacting the IRT system. Study drug replacements and an explanation of the reason for the misplaced or damaged study drug will be documented within the subject's source record. Date of the first dose and the last dose of palivizumab injection will be documented in the subject's source and recorded on the appropriate eCRF page.

The investigator and designees agree not to supply study medication outside the context of this study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a prospective, multicenter, open-label, non-comparative clinical study, designed to collect further data on safety and effectiveness of palivizumab solution for injection when administered as RSV prophylaxis to high-risk infants in the Russian Federation and the Republic of Belarus to meet regulatory requirements of the Russian Ministry of Health.

5.6.2 Appropriateness of Measurements

Regular vital signs measurements (HR, BP, RR and body temperature), physical examinations and weight measurements will be performed to ensure subject's safety. These measurements used in this study are currently accepted methods of assessing pediatric subjects.

All hospitalizations will be assessed in terms of relationship to RSV to ensure the quality of primary variable data collection. Cardiac/respiratory illness as the cause of hospitalization or deterioration of subject's condition during ongoing hospitalization will be regarded as potentially related to RSV, and in these subjects, an RSV diagnostic test will be performed.

5.6.3 Suitability of Subject Population

This study plans to enroll children who are at high risk of infection with RSV leading to severe lower respiratory tract disease. Infants and children born prematurely, those with BPD, and those with hemodynamically significant CHD are particularly vulnerable to RSV infection. RSV is more likely to progress to the lower respiratory tract and cause more serious disease in these high-risk children. Furthermore, the course of illness tends to be more severe in these children, and is associated with higher rates of hospitalization. This patient population has been the target population studied in the development of palivizumab which is currently approved for prophylaxis of serious disease caused by respiratory syncytial virus (RSV) infection for the indicated high-risk paediatric populations.

5.6.4 Selection of Doses in the Study

The dose of palivizumab selected for this study is 15 mg/kg by IM injection every 30 days. Numerous clinical trials conducted in high-risk children infected with RSV during the development program have shown palivizumab to be safe and well tolerated at doses of 15 mg/kg. This dose is also the approved dose for use in the prevention of serious lower respiratory tract disease caused by RSV in children at high-risk for RSV

disease which is supported by the safety and efficacy results demonstrated in the pivotal pediatric Phase 3 trials.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.5. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject An event that results in the death of a subject.

Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

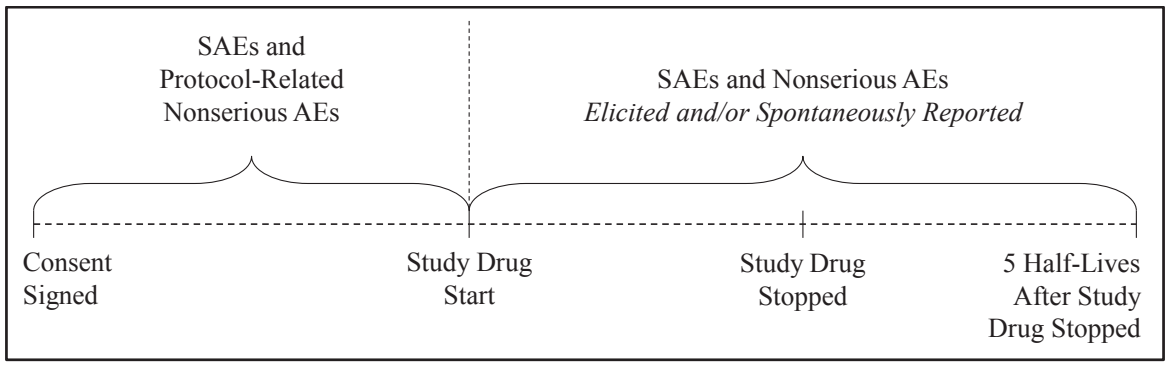
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause(s) of event must be provided by the investigator for the adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events will be collected from the time the parent(s)/legal guardian(s) signed the study-specific informed consent until study drug administration. From the time of study drug administration until 5-half-lives (100 days) following discontinuation of study treatment has elapsed, all adverse events and serious adverse events will be collected, whether solicited or spontaneously reported by the parent(s)/legal guardian(s).

Adverse event information will be collected as shown in Figure 1.

Figure 1. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Antiviral Safety Team at:

[redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Since the study is only conducted in infants, information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will not be collected.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events that occur during the study will be managed and followed by the investigator as clinically indicated. A drug-related toxicity is an adverse event that is judged by the investigator to have a "reasonable possibility" of being related to the study drug (Section 6.1.3).

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact: Alternate Contact:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Data will be summarized using SAS (SAS Institute, Inc.). Since this is a non-controlled study, only descriptive analyses will be provided. 95%-confidence intervals will be provided as appropriate.

8.1.1 Data Set Analyzed

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

8.1.2 Demographics, Other Baseline Characteristics, and Risk Factors

Data will be summarized descriptively. For continuous variables, the mean, standard deviation, median, minimum and maximum values will be calculated. For categorical variables, the number and percentage of subjects in each category within an assessment will be calculated for non-missing data.

Other medications used prior to study drug initiation and continued during the study or initiated during the study will be summarized with frequencies and percentages.

8.1.3 Primary Endpoint (RSV-Hospitalization)

The primary analysis will be the calculation of the number and proportion of subjects with RSV-hospitalization along with the 95% exact confidence interval for the proportion. 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) deaths, which can be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence). 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 within 30 days of the last study drug dose will be included in the analyses for the primary endpoint.

8.1.4 Secondary Endpoints (Morbidity)

Length of hospital stay, use and duration of oxygen supplementation, use and duration of mechanical ventilation, and admission to and duration of ICU will be summarized descriptively for all subjects with RSV hospitalization (including new onset of nosocomial respiratory/cardiac symptoms). For continuous variables, the mean, standard deviation, median, minimum and maximum values will be calculated. For categorical variables, the number and percentage of subjects in each category within an assessment will be calculated for non-missing data. 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.

8.1.5 Study Drug Exposure

The number and percentage of subjects receiving 1, 2, 3, 4, 5 and more than 5 doses of study drug will be calculated.

8.1.6 Adverse Events

Adverse events will be coded using the current version of MedDRA (Medical Dictionary for Regulatory Activities), International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva, Switzerland. Treatment-emergent adverse events will be defined as those occurring after study drug initiation and within 100 days after the last dose of study drug.

The following subgroups of treatment-emergent adverse events will be summarized with frequencies and percentages by System Organ Class and Preferred Term: all events; events with probable, possible, or unknown relationship to study drug; events resulting in death; serious adverse events; and events resulting in study discontinuation. In these analyses, each subject will be counted no more than once for each Preferred Term.

Treatment-emergent adverse events will also be summarized with frequencies and percentages using the following groupings of adverse events: by System Organ Class, Preferred Term and severity; and by System Organ Class, Preferred Term and relationship to study drug. For analyses by severity, the most severe adverse event for each Preferred Term will be selected for each subject. For analyses by relationship to study drug, the event with the strongest relationship to study drug for each Preferred Term will be selected for each subject.

8.1.7 Vital Signs

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

Change from baseline to each visit for each vital sign and weight variable will be summarized. For the analyses of the mean change from baseline to each study visit,

baseline values will be defined to be the final measurement obtained prior to study drug initiation. For vital sign variables, values collected after the study drug injection on the visit day will be excluded from the analyses. The change from baseline will be defined as the difference between the value at each visit and the baseline value. If a subject has more than 1 value in a particular visit window, the value obtained nearest to the appropriate visit day will be used. Visit windows are defined in Table 1. The analysis at each visit will include only those subjects with both a baseline value and a value obtained at the visit. Baseline and visit values and changes from baseline will be summarized with means and standard errors; changes from baseline will be tested using paired t-tests.

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.

8.2 Determination of 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. However, 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.

8.3 Randomization Methods

This is not applicable for this study, as this is an open label, non-comparative study.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of

subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the parent(s)/legal guardian(s), and answer all questions regarding this study. Prior to any study-related procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the parent(s)/legal guardian(s), the person who administered the informed consent, and any other signatories according to local

requirements. For children with 2 parents, at least one must sign the consent, stating that the other parent does not object. A copy of the informed consent form will be given to the subject's parent(s)/legal guardian(s), and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the parent(s)/legal guardian(s) received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

The study patient card should be provided to the subject's parent(s)/legal guardian(s) after the informed consent process.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being

collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

All information concerning palivizumab and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of palivizumab. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial related monitoring, audits, IEC/IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie.

Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's follow-up contact, which is defined as 100 days following the final injection of palivizumab.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Synagis® (Palivizumab).
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	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
Protocol Date:	25 May 2016

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Medical Safety Evaluation
		Statistics
		Regulatory
		Clinical

Appendix C. Study Activities

Activity	Visit 1 Enrollment	Visit 2	Visit 3	Visit 4[a]	Visit 5[b]/ET	Follow-Up Contact 1[c]	Follow-Up Contact 2[c]
Timelines and Allowance Window[d]	**Day 0 Baseline**	**Day 30 (–5 Days)**	**Day 60 (±5 Days)**	**Day 90 (±5 Days)**	**Day 120 (±5 Days)**	**Last Prophylaxis Visit + 30 Days (+5 Days)**	**Last Prophylaxis Visit + 100 Days (+5 Days)**
Informed Consent	X						
Provide subject card	X						
Medical and Birth History	X						
Prior[e]/Concomitant Medication	X	X	X	X	X	X	X
In-/Exclusion Criteria	X						
Assignment of Subject Number	X						
Demographics and Social History	X						
Physical Examination & Weight	X	X	X	X	X		
Body Length/Height	X						
Vital Signs[f] (HR, BP, RR, T°C)	X	X	X	X	X		
Monitor Adverse Events[g]	X[g]	X	X	X	X	X	X
Study Drug administration[h]	X[h]	X	X	X	X		
RSV Diagnostic Test[i]	X						
Assessment of RSV-Hospitalizations		X	X	X	X	X	

ET = Early Termination

a. Only applicable to subjects enrolled during November 2016 through December 2016.

b. Only applicable to subjects enrolled during November 2016.

c. Telephone contact by Investigator/designee.
d. Allowance window is given in parentheses.
e. Will be collected for medications given 2 weeks prior to enrollment.
f. Vital signs to be measured prior to and 30 minutes after administration of study drug.
g SAEs to be registered from the time the study informed consent is signed.
h. Only applicable to subjects fulfilling Inclusion/Exclusion Criteria.
i. In case of a cardiac/respiratory hospitalization or deterioration in cardiac/respiratory status in a hospitalized infant, an RSV diagnostic test will be done as soon as possible, but not later than 48 hours of hospitalization.

Appendix D. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.1 Synopsis
Subsection Objective:
First sentence previously read:

To assess the 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.

Has been changed to read:

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.

Section 1.1 Synopsis
Subsection Statistical Methods:
Heading "Sample Size:"
First sentence previously read:

The objective of this study is to describe the effectiveness and safety of the liquid formulation of palivizumab in young children at high risk of severe RSV disease in the Russian Federation and the Republic of Belarus.

Has been changed to read:

The objective of this study is to collect further data on the effectiveness and safety of the liquid formulation of palivizumab in young children at high risk of severe RSV disease in the Russian Federation and the Republic of Belarus.

Section 3.0 Introduction
Tenth paragraph previously read:

This international, multicenter, open-label study is intended to examine the safety and effectiveness of palivizumab solution for injection in children at high risk of severe respiratory syncytial virus infection in the Russian Federation and the Republic of Belarus.

Has been changed to read:

This international, multicenter, open-label study is intended to collect further data on the safety and effectiveness of palivizumab solution for injection in children at high risk of severe respiratory syncytial virus infection in the Russian Federation and the Republic of Belarus.

Section 3.1 Differences Statement
Last sentence previously read:

This study will further describe the safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population.

Has been changed to read:

This study will collect further data on safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population.

Section 3.2 Benefits and Risks
First sentence previously read:

The present study is a prospective, multicenter, open-label, non-controlled study to describe safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population of preterm infants, infants with chronic lung disease (CLD) of prematurity and infants with hemodynamically significant congenital heart disease (CHD).

Has been changed to read:

The present study is a prospective, multicenter, open-label, non-controlled study to collect further data on safety and effectiveness of palivizumab solution for injection in the Russian and Belarusian population of preterm infants, infants with chronic lung disease (CLD) of prematurity and infants with hemodynamically significant congenital heart disease (CHD).

Section 4.0 Study Objective
Previously read:

The objective of this study is to describe the safety and effectiveness of palivizumab solution for injection administered as monthly intramuscular injections among preterm infants (≤ 35 wGA), infants with CLD of prematurity and infants with hemodynamically significant CHD in the Russian Federation and the Republic of Belarus.

Has been changed to read:

The objective of this study is to collect further data on safety and effectiveness of palivizumab solution for injection administered as monthly intramuscular injections among preterm infants (≤ 35 wGA), infants with CLD of prematurity and infants with hemodynamically significant CHD in the Russian Federation and the Republic of Belarus.

Section 5.6.1 Discussion of Study Design and Choice of Control Groups
Previously read:

This is a prospective, multicenter, open-label, non-comparative clinical study, designed to describe the safety and effectiveness of palivizumab solution for injection when administered as RSV prophylaxis to high-risk infants in the Russian Federation and the Republic of Belarus to meet regulatory requirements of the Russian Ministry of Health.

Has been changed to read:

This is a prospective, multicenter, open-label, non-comparative clinical study, designed to collect further data on safety and effectiveness of palivizumab solution for injection when administered as RSV prophylaxis to high-risk infants in the Russian Federation and the Republic of Belarus to meet regulatory requirements of the Russian Ministry of Health.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Medical Safety Evaluation
		Statistics
		Regulatory
		Clinical

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Medical Safety Evaluation
		Statistics
		Regulatory
		Clinical

Document Approval

Study M15539 - 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 Belarus - Amendment 1 - EudraCT 2016-000221-39 - 25May2016

Version: 1.0 **Date:** 29-May-2016 09:41:03 AM **Company ID:** 05292016-00F9F68124E255-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	25-May-2016 08:59:13 PM	Approver
	25-May-2016 09:01:06 PM	Approver
	25-May-2016 09:02:10 PM	Approver
	26-May-2016 11:49:44 A	Approver
	27-May-2016 07:34:03 AM	Approver
	29-May-2016 09:41:00 AM	Approver