2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For national Authority Use Only)**
Name of Study Drug: Palivizumab	**Volume:**	
Name of Active Ingredient: Palivizumab	**Page:**	
Title of Study: A Prospective, Multicenter, Open-Label, Non-Comparative Study of Safety and Efficacy of Synagis® in Children at High Risk of Severe Respiratory Syncytial Virus Infection in the Russian Federation		
Investigator: [redacted]		
Study Site(s): redacted information 24Sep2014 Multicenter trial conducted at 19 centers in the Russian Federation		
Publications: None		
Studied Periods: Date of first subject first dose: 05 November 2009 Date of last subject last dose: 01 April 2010		**Clinical Phase:** 2–3
Objectives: The objective of this study was to describe the safety and efficacy of palivizumab in the prevention of severe RSV infection in preterm infants (≤ 35 wGA), infants with bronchopulmonary dysplasia and infants with hemodynamically significant congenital heart disease in the Russian Federation.		
Methodology: This was a Phase 2 to 3, prospective, multicenter, open-label, non-comparative clinical study of immunoprophylaxis with palivizumab for the prevention of severe lower respiratory tract RSV infection in infants at high risk. Approximately 100 subjects were to be enrolled into the study in the Russian Federation. Recruitment was to start November 2009 and continue no later than 31 January 2010. All enrolled subjects had to undergo monthly visits with safety assessments and administration of palivizumab IM 15 mg/kg for passive immune protection during the RSV season defined as November 2009 through March 2010. All subjects enrolled were to be followed by a telephone contact 30 and 100 days after last injection. All respiratory/cardiac hospitalizations or deterioration in the respiratory/cardiac status in a hospitalized subject were to be evaluated with a diagnostic test for RSV (rapid immunochromatographic) to determine if RSV contributed to the hospitalization or deterioration.		

Number of Subjects (Planned and Analyzed):

Planned: A total of 100 subjects were planned to be enrolled to receive passive immunization against RSV infection with palivizumab during the 2009/2010 RSV season in the Russian Federation (November 2009 to March 2010).

Analyzed: As planned, 100 subjects were enrolled and constituted the intent-to-treat analysis set. Among those 100 subjects, 2 subjects violated inclusion criterion 1 (subjects at high risk of severe RSV infection), one subject violated exclusion criterion 11 (exclusion of prior administration of RSV vaccine or prophylaxis). In total, 94 subjects completed the study as planned, while 6 withdrew prematurely (1 due to an adverse event, 1 due to refusal to participate, and 4 because of parent(s) being unable/not willing to perform onsite visits).

Diagnosis and Main Criteria for Inclusion: Infants at high risk of severe RSV infection defined as preterm infants born ≤ 35 weeks gestational age and ≤ 6 months of age at enrollment; or infants ≤ 24 months of age at enrollment with a diagnosis of bronchopulmonary dysplasia (BPD) requiring intervention/management any time within 6 months prior to enrollment; or infants ≤ 24 months at enrollment with hemodynamically significant congenital heart disease (HSCHD).

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Palivizumab is a humanized monoclonal immunoglobulin derived from the NSO cell line and specific for the F protein of RSV. Palivizumab was provided in 5 mL single-use glass vials designed to deliver 100 mg of palivizumab in 1.0 mL (100 mg/mL) when reconstituted with 1.0 mL of sterile water for injection. Palivizumab was administered by intramuscular injection in doses of 15 mg/kg body weight.

Lot Number: [redacted] redacted information 24Sep2014

Duration of Treatment: Palivizumab was to be administered every 30 days, beginning at the time of enrollment in November or December 2009 or January 2010, through March 2010. Depending on the month of enrollment, November, December or January, subjects were to receive 5, 4 or 3 injections, respectively.

Reference Therapy: None.

Criteria for Evaluation

Efficacy:

Primary efficacy endpoint

The primary efficacy variable in this study was hospitalization due to RSV infection.

Respiratory and cardiac hospitalization was defined as hospitalization occurring in a time frame from the first dose of study drug until 30 days (+ 5 days) after the last injection, with primary reason for hospital admission being evaluation or treatment of a respiratory/cardiac condition. Also, the new onset of respiratory/cardiac symptoms in an already hospitalized subject, with an objective measure of worsening respiratory/cardiac status was rated a respiratory/cardiac hospitalization.

RSV hospitalization was defined as either: 1) a respiratory/cardiac hospitalization with a positive RSV test, 2) the new onset of respiratory/cardiac symptoms in an already hospitalized subject, with an objective measure of worsening respiratory/cardiac status and a positive RSV test, or 3) death, that could be demonstrated as caused by RSV (by autopsy, clinical history, or virologic evidence). RSV hospitalizations were registered from the time of the first dose until 30 days (+ 5 days) after the last injection of palivizumab.

Criteria for Evaluation

Efficacy (Continued):

Secondary efficacy endpoints

Secondary efficacy variables were:

- Total number of days of hospitalization due to RSV infection
- Days of hospitalization due to RSV infection with increased supplemental oxygen requirement
- Number of admissions to intensive care (ICU) during hospitalization due to RSV infection
- Total days of ICU stay due to RSV infection
- Number of subjects with mechanical ventilation during hospitalization due to RSV infection
- Total days of mechanical ventilation during hospitalization due to RSV infection

Safety:

Safety and tolerability of palivizumab were assessed by summarizing adverse events occurring from enrollment until 100 days following the last injection of study drug. In addition, vital signs and physical findings were obtained at each visit, both pre- and post-injection.

Statistical Methods: No formal sample size calculation was performed. It was determined prior to the start of the study, that approximately 100 treated subjects would provide sufficient data.

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

All analyses were performed as intent-to-treat (ITT), defined as enrolled subjects who received at least one dose of study drug.

Summary/Conclusions

Baseline Parameters: All 100 subjects were enrolled in either November (64 subjects) or December (36 subjects) 2009 of which 48/100 (48%) were male and 52/100 (52%) were female. Ninety eight (98) enrolled subjects fulfilled the requirements for subjects at high risk of severe RSV infection, defined as born prematurely (≤ 35 wGA) and younger than 6 months at the time of enrollment or suffering from bronchopulmonary dysplasia (BPD) of prematurity or hemodynamically significant congenital heart disease (HSCHD) and younger than 24 months at the time of enrollment. Two subjects, who both were both born preterm and had BPD, did not meet inclusion criterion because they were born after 36 wGA and thus did not meet the either the preterm criteria (≤ 35 wGA) or BPD criteria for requiring oxygen at 36 wGA. Mean gestational age was 33.4 weeks (SD 5.1) ranging from 24 to 42 weeks. Mean birth weight was 2.14 kg. As to the medical history, respiratory distress syndrome/bronchopulmonary dysplasia was seen in 52/100, and congenital heart disease in 41/100 subjects. A pathological murmur was found in 30/100 subjects. For 78/100 subjects the conditions diagnosed were symptomatic at baseline or requiring treatment, among them 34/100 subjects with respiratory distress syndrome/bronchopulmonary dysplasia, and 33/100 subjects with hemodynamically significant congenital heart disease.

Efficacy Results: During the entire study period there was no case of RSV hospitalization. An RSV test (rapid immunochromatographic) was performed in 6 of 7 subjects experiencing a respiratory/cardiac hospitalization, but was negative in all cases. One subject did not have an RSV test performed. Since there were no cases of RSV hospitalization, the planned secondary efficacy parameters could not be evaluated.

Safety Results:

The total number of doses administered is presented below:

Total Number of Doses Administered						
	1	2	3	4	5	6
n (%)	3 (3.0)	1 (1.0)	3 (3.0)	26 (26.0)	65 (65.0)	2 (2.0)

The planned number of doses depended on whether the subject was enrolled in November (64) or December (36). Two subjects enrolled in December received 6 doses of palivizumab due to additional doses following cardiopulmonary bypass during cardiac surgery. In total, 4 of 15 subjects who underwent cardiopulmonary bypass during cardiac surgery received an additional dose of palivizumab. Six (6) subjects terminated the study prematurely prior to the fourth administration of study drug, and a seventh subject did not receive their fourth dose due to an in-hospital SAE following cardiac surgery, extending the dosing period outside the RSV season. The total amount of palivizumab administered in the study ranged from 47 to 1022 mg with a mean of 516.5 mg (SD 192.3, median 507.5 mg).

Safety Results (Continued)

Eighty (80) treatment-emergent adverse events (TEAEs) were documented in 41 of 100 subjects (41%) through 30 days following the last injection. During the period of 100 days after last injection, 84 TEAEs occurred in 44/100 subjects (44%). One non-serious TEAE (atopic dermatitis) led to discontinuation of the study drug. This event was assessed as mild in severity and possibly related to study drug.
Three TEAEs in 3 subjects were rated as severe in intensity: one case each of arrhythmia, pneumonia and tonsillitis, all assessed as not related to study drug. Three TEAEs in 2 subjects were assessed as possibly related (acute intermittent rhinitis and rhinitis, both in one subject, and atopic dermatitis). All other AEs/TEAEs were assessed as mild or moderate, and as not related or probably not related to study drug.

In total, 12 TESAEs occurred in 10 subjects, mainly coded as infectious diseases (7 subjects) such as bronchitis, enteritis, tonsillitis, or pneumonia. All TESAEs were, however, categorized as being not related to study drug.

No clinically relevant changes in vital signs were seen when comparing mean visit values (pre-injection) versus baseline (Visit 1; Day 0). Neither were there significant changes when comparing vital sign values measured prior to and following injection of the study drug. Body weight increased with age as expected.

Conclusions: Palivizumab, administered as repeated injections every 30 days throughout the winter RSV season of 2009/2010 at multiple sites throughout the Russian Federation, was found to be safe and well tolerated in this mixed population of subjects at risk for serious RSV infection. In addition, there were no RSV hospitalizations reported through 30 days following the final injection of palivizumab. Thus, the safety and effectiveness of palivizumab was confirmed in a small mixed population of Russian subjects at risk for serious RSV infection.

Date of Report: 22 December 2010