2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Palivizumab		
Name of Active Ingredient: Palivizumab		

Title of Study: 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

Coordinating Investigator: [redacted]

Study Sites: 7 sites in the Russian Federation and the Republic of Belarus

Publications: 0

Studied Period (Years): First Subject First Visit: 09 November 2016 Last Subject Last Visit: 13 July 2017	**Phase of Development:** 3b

Objective:

The objective of this study was to collect further data on safety and effectiveness of the liquid formulation of palivizumab administered as monthly intramuscular (IM) injections among preterm infants, infants with bronchopulmonary dysplasia (BPD), and infants with hemodynamically significant congenital heart disease (HSCHD) in the Russian Federation and the Republic of Belarus.

Methodology:

Study M15-539 was a Phase 3b, prospective, multicenter, open-label (OL), non-controlled clinical study of immunoprophylaxis with the liquid formulation of palivizumab for the prevention of severe lower respiratory tract RSV infection in infants at high-risk of severe RSV infection (preterm infants, infants with BPD, and infants with HSCHD) during the 2016 – 2017 RSV season (November 2016 through March 2017).

All cardiac/respiratory hospitalizations or deterioration in the cardiac/respiratory status in a hospitalized infant were evaluated by testing nasopharyngeal specimens with a validated real-time respiratory syncytial virus (RSV) diagnostic test (real-time reverse transcription polymerase chain reaction [RT-PCR]) of respiratory secretion specimens (nasopharyngeal swab, nasopharyngeal aspiration, or lavage) to determine if RSV contributed to the hospitalization or deterioration.

Number of Subjects (Planned and Analyzed):

Planned – 50 subjects; analyzed – 50 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in this study were male or female infants who were born preterm (≤ 35 weeks gestational age [wGA]) and ≤ 6 months of age at enrollment; and/or were ≤ 24 months of age at enrollment with a diagnosis of BPD (defined as oxygen requirement at a corrected wGA of 36 weeks) requiring intervention/management (i.e., oxygen, diuretics, bronchodilators, corticosteroids, etc.) within the 6 months prior to enrollment; and/or were ≤ 24 months of age at enrollment with HSCHD (either cyanotic or acyanotic; unoperated or partially corrected). Children with acyanotic cardiac lesions must have had pulmonary hypertension (≥ 40 mmHg measured pressure in the pulmonary artery) or the need for daily medication to manage HSCHD.

Subjects were not to be enrolled if they had any of the following conditions: hemodynamically insignificant small atrial or ventricular septal defects, patent ductus arteriosus, aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone. Subjects were also excluded if at the time of enrollment they had been hospitalized or were using mechanical ventilation (including continuous positive airway pressure [CPAP]), had a life expectancy of < 6 months, had unstable cardiac or respiratory status (including severe cardiac defects), had active respiratory illness or other acute infections, or had known renal or hepatic impairment.

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

Palivizumab (concentration 100 mg/mL) solution for injection in 1 mL vials; 15 mg/kg IM injection; lot number 16-004131.

Duration of Treatment: A minimum of 3 and a maximum of 5 months (1 injection/month)

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable; non-controlled OL study.

Criteria for Evaluation

Effectiveness:

Number of subjects with RSV hospitalization (primary variable) and, for subjects with RSV hospitalization, the total number of hospitalization days, number of subjects requiring 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] or increased mechanical ventilation total number of hospitalization days with use of increased supplemental oxygen or increased mechanical ventilation, and number and duration of intensive care unit (ICU) hospital stays (secondary variables).

Safety:

Adverse event (AE) collection and vital signs (including blood pressure [BP; supine body position], pulse, respiratory rate (RR), temperature [°C]), and height/length/body weight [BW] measurements).

Statistical Methods

Effectiveness:

Since Study M15-539 was a non-controlled study, only descriptive analyses were provided. All analyses were performed on the intent-to-treat (ITT) analysis set, defined as all enrolled subjects who received at least 1 dose of study drug. The primary analysis was the calculation of the number and proportion of subjects with RSV-hospitalization (including new onset of nosocomial respiratory/cardiac symptoms), along with the 95% exact confidence interval (CI) for the proportion. Length of hospital stay, use and duration of oxygen supplementation, use and duration of mechanical ventilation, and admission to and duration of ICU were to be summarized descriptively for all subjects with RSV hospitalization (including new onset of nosocomial respiratory/cardiac symptoms).

Safety:

Treatment-emergent AEs (TEAEs) with an onset date ≤ 30 or 100 days after the last dose of study drug were summarized using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms (PTs) according to MedDRA version 20.0. TEAEs were summarized by frequency, relationship to study drug (rated by the investigator to have reasonable/no reasonable possibility of being related to study drug), severity, and seriousness. TEAEs leading to discontinuation of study drug or death were also tabulated. Subjects reporting more than one TEAE for a given PT were counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of TEAE were counted only once in the overall total.

Vital signs parameters (see list in above section) were assessed prior to and 30 minutes after study drug administration, with the exception of BW, which was only measured prior to study drug administration. Mean changes from baseline in vital signs at each study visit were summarized quantitatively and analyzed descriptively using a paired t-test. For analyses of changes from baseline, only those subjects with values both at baseline and at the respective visit were included. For each vital sign variable, mean changes from pre-injection value to post-injection value at each visit were also summarized and analyzed using a paired t-test.

Summary/Conclusions

Effectiveness Results:

No subjects experienced hospitalization for RSV infection during the study while being treated prophylactically with the liquid formulation of palivizumab. Five subjects were hospitalized and tested for RSV infection during the study, but none had RSV infection. Since no RSV hospitalizations were reported at any point during this study, the prophylactic use of the liquid formulation of palivizumab was considered to be effective in preventing serious disease due to RSV infection requiring hospitalization in subjects 24 months of age or less with prematurity, BPD, or HSCHD.

Safety Results:

No deaths were reported in the study. TEAEs were reported in 11 subjects (22.0%) within 30 days of last study drug administration, and no additional TEAEs were reported > 30 days after last study drug administration. No subjects experienced TEAEs of RSV infection in the study. Treatment-emergent serious AEs (SAEs) were reported in 6 subjects (12.0%), but all were considered to be unrelated to study drug. One SAE of tachycardia paroxysmal was the only severe event reported. One SAE of hemangioma was the only event that led to discontinuation of study drug. The AEs reported in the study were not unexpected given the background medical conditions in the patient populations studied (i.e., subjects with prematurity, BPD and/or HSCHD) and indicated for palivizumab prophylaxis.

Summary/Conclusions (Continued)

Conclusions:

The liquid formulation of palivizumab, administered prophylactically every 30 days during the 2016/2017 RSV season in the Russian Federation and the Republic of Belarus, was considered to effectively protect subjects at high risk of contracting serious RSV infection due to prematurity, BPD, or HSCHD from hospitalization due to an RSV infection during the study. In addition, this formulation of palivizumab was found to be safe and well tolerated in all subjects, consistent with the known safety profile of palivizumab. No new safety signals were identified. These results in this mixed population of subjects at risk for serious RSV infection support the approval of the palivizumab liquid formulation in the Russian Federation and the Republic of Belarus.