



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Item of the Submission:	(For National Authority Use Only)
Name of Study Drug: Synagis [®]	Volume:	
Name of Active Ingredient: Palivizumab	Page:	
Title of Study: A Phase IV, Multicenter, Comparative Study in Preterm Children Who Previously Received Synagis [®] Prophylaxis Versus Preterm Children Without RSV Prophylaxis: Development of Reactive Airway Disease		
Investigators: Twenty-seven sites in Canada, Germany, Netherlands, Poland, Spain, and Sweden		
Study Sites: Multicenter		
Publications: Simoes EAF, Carbonell-Estrany X, Kimpen J, Rieger CHL, Morris DD, Pollack PF, et al. Palivizumab use decreases risk of recurrent wheezing in preterm children. Eur Respir J. 2004;24 (Suppl 48):212s.		
Studied Period (Years): Initiation Date: July 10, 2001 Completion Date: October 8, 2004	Phase of Development: 4	
Objective: To determine whether Synagis [®] prophylaxis in prematurely born children leads to a decrease in the incidence and degree of Reactive Airway Disease (RAD) episodes as compared with two matched control groups: one control group with at least one documented Respiratory Syncytial Virus (RSV) hospitalization in their first year of life and never having received Synagis [®] , and a second control group having no documented RSV hospitalizations and never having received Synagis [®] .		
Methodology: W00-353 was a prospective, case-controlled, observational study evaluating the effect of Synagis [®] prophylaxis in decreasing the incidence and degree of RAD episodes in preterm children. All subjects were ≤36 months of age at the time of enrollment, born prematurely (≤35 weeks gestational age), and had no history of Chronic Lung Disease (CLD), defined as chronic lung disease of preterm infants with respiratory insufficiency and requiring oxygen therapy at 36 weeks gestation. Subjects were enrolled and matched onsite from 3 groups: Group 1 had previously received Synagis [®] ; Group 2 never received Synagis [®] and had at least one documented RSV hospitalization during the first year of life; and Group 3 never received Synagis [®] and never had a documented RSV hospitalization. Controls were matched based on gestational age ± 4 weeks, gender (where possible), and year of delivery ± 3 months.		



Subjects were evaluated prospectively for 24 months following study enrollment. Monthly assessments were completed during scheduled clinic visits and telephone interviews.

During each visit, a standardized respiratory questionnaire, which was designed to identify interim changes in respiratory status, was administered; a physical examination (including vital signs, weight, and chest examination) was also performed. Furthermore, during Visit 1 (baseline), a full medical history was obtained and blood drawn for serum RSV-neutralizing antibody and IgE antibody evaluation. At each subsequent visit, an interval medical history was obtained and adverse events were recorded.

Number of Subjects (Planned and Analyzed):

Planned (N) = 300

Analyzed (N) = 421

Diagnosis and Main Criteria for Inclusion:

Subjects who participated in the study were ≤ 36 months of age at enrollment, had been born prematurely (≤ 35 weeks gestational age), and had no history of CLD. Participants had either previously received Synagis[®] (Group 1), had never received Synagis[®] and had at least one documented RSV hospitalization during their first year of life (Group 2), or had never received Synagis[®] and never had a documented RSV hospitalization (Group 3).

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

This study was designed as a follow-up study for children who previously received Synagis[®]. No study drug was administered.

Duration of Treatment:

Subjects were observed for 24 months following study enrollment.

Reference Therapy, Dose and Mode of Administration, and Lot Number:

No study drug was administered.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the incidence of recurrent wheezing, defined as 3 or more episodes of bronchial obstruction within the 24-month observation period. The primary comparison was the Synagis[®] group with the combined control groups. Secondary efficacy variables included the incidence of asthma, any wheezing, and respiratory hospitalization.

Safety:

Adverse events were collected during telephone contacts and at scheduled visits. Vital signs were measured and physical examinations performed at specified visits throughout the study period.

Statistical Methods:

Efficacy:

All enrolled subjects who were in the study for at least 2 days were included in the statistical analyses. Unless otherwise specified, statistical tests were two-tailed at the $\alpha=0.05$ level of significance and P-values were rounded to 3 decimal places. The primary efficacy parameter was comprised of the number and proportion of subjects who developed recurrent wheezing, summarized by group. The percentage was then compared between the Synagis[®] group and the combined control groups using Fisher's exact test. As a secondary analysis, the proportion of Synagis[®] subjects who developed recurrent wheezing



was compared to each of the control groups separately. These same methods were used to analyze the endpoints of respiratory hospitalization, any wheezing, and asthma. Logistic regression was used to evaluate the predictive value of baseline characteristics on the occurrence of respiratory hospitalization, recurrent wheezing, any wheezing, and asthma. A proportional hazards regression model was used to evaluate the predictive value of baseline characteristics on time to respiratory hospitalization, recurrent wheezing, any wheezing, and asthma.

Safety:

Descriptive summaries of all adverse events (AEs) and vital signs are provided, but no statistical tests were performed. The incidence of serious adverse events (SAEs) resulting in hospitalization was compared between the Synagis® group and each of the control groups using Fisher's exact test.

Efficacy Results:

Statistically significantly lower percentages of Synagis® subjects experienced recurrent wheezing, any wheezing, and asthma, compared with control subjects. Furthermore, as shown in a multiple logistic regression analysis, Synagis® subjects had a statistically significantly lower incidence rate of recurrent wheezing and asthma, after adjustments for other significant factors. Subjects in the Synagis® group also had statistically significantly longer time to recurrent wheezing and asthma, as shown in a proportional hazards regression model. The number of days spent in the hospital per 100 child years was statistically significantly less for Synagis® subjects compared with control subjects. The incidence of corticosteroid use was also statistically significantly lower for subjects in the Synagis® group.

Safety Results:

The most common AEs (≥5%) in the Synagis® group were infection, reaction unevaluable, bronchitis, and pharyngitis. Most AEs were mild or moderate in intensity and were judged by the Investigator as probably not related or not related to the study. Two deaths were reported during the study period; one in Group 1 and one Group 3. Both were judged as not related to the study. Most SAEs were considered serious because they resulted in hospitalization; all SAEs were judged as not related to the study. The incidence of hospitalization due to SAEs for the Synagis® group was similar compared with each of the control groups.

Summary:

Synagis® prophylaxis was associated with statistically significantly lower percentages of subjects who experienced recurrent wheezing, any wheezing, and asthma during the study period. In addition, subjects in the Synagis® group had a statistically significantly lower incidence of corticosteroid use for wheezing/asthma, and a statistically significantly less number of days spent in the hospital per 100 child years compared with control subjects. Based on the safety assessments, Synagis® did not contribute to the occurrence of AEs in subjects who previously received the drug.

Conclusion:

As evidenced by the study results, Synagis® prophylaxis may have the potential to reduce the incidence and degree of recurrent wheezing in preterm children at risk for RSV infection.

Report Date: 3 August 2005