2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td>Individual Study Table Referring to Part of Dossier:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Palivizumab</td><td>Volume:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
Palivizumab</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study:
A Phase IV, Case-Matched, Cohort Surveillance Study in Preterm Children Who Receive SYNAGIS® Prophylaxis in the First Year of Life Versus Preterm Children Without RSV Prophylaxis: Incidence of RSV Hospitalization and Assessment of Disease Severity in the Season Following Prophylaxis</td></tr>
<tr><td colspan="3">Investigators/Study Sites:
87 study sites in Austria, Canada, Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Portugal, Spain, and Sweden</td></tr>
<tr><td colspan="3">Publications:
None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Visit: 15 May 2003
Final Visit: 19 May 2005</td><td>Phase of Development: 4</td></tr>
<tr><td colspan="3">Objective:
The primary objective was to determine if the incidence of hospitalization for respiratory syncytial virus lower respiratory tract infection (RSV-LRTI) in infants who have or have not received palivizumab (SYNAGIS) prophylaxis in their first RSV season differed in the subsequent respiratory season. The purpose of this study (M02-489) is to provide the EMEA with an acceptable degree of confidence that those children who received SYNAGIS are not at an increased risk for hospitalization with severe RSV in the subsequent respiratory season.</td></tr>
<tr><td colspan="3">Methodology:
Study M02-489 was a Phase IV, case-matched, cohort surveillance study of preterm children who received SYNAGIS prophylaxis in the first year of life (SYNAGIS) vs. preterm children without any RSV prophylaxis (Control).
Subjects were followed over their second RSV season. The study was conducted through two RSV seasons. SYNAGIS subjects were matched to Control subjects. Matching of subjects was season-specific, and was performed each study period using the following criteria:
1. Postmenstrual age (33 to 35 weeks gestation, 29 to 32 weeks gestation, or ≤ 28 weeks gestation)
2. Month of birth ± 3 months
3. Gender (whenever possible)</td></tr>
</table>

A potential control subject was identified by location and matched with a SYNAGIS-treated subject, based on the criteria above by one of three options:

- Within the individual study sites (if possible)
- Between investigative sites within the country (if possible)
- Between the investigative sites from any of the participating countries (if the first two options were unsuccessful)

Subjects that could not be matched were to be screen-failed.

Throughout the study, data were collected by an interval medical and environmental questionnaire, and by subsequent evaluation of the subject's medical records for serious adverse events (SAEs) and incidence of RSV hospitalizations.

Study M02-489 data were combined with data from Studies W99-311 and W00-353 for the primary analyses of subject disposition, demographics and Baseline characteristics, the majority of the efficacy analyses (incidence of RSV+ hospitalization), and the primary SAE analysis. Study W99-311 is a completed study with two treatment groups, SYNAGIS and Control. Study W00-353 is a completed study with three treatment groups, SYNAGIS and two Control groups, but only the SYNAGIS group and the Control group with no documented RSV hospitalization before study entry were included for analysis.

Number of Subjects (Planned and Analyzed):

Planned (Study M02-489): At least 1250-1300 matched subjects (625-650 subjects per group)

Analyzed (Study M02-489): 684 per group for the primary efficacy analysis and 704 per group for the primary SAE analysis

Diagnosis and Main Criteria for Inclusion:

Subjects were required to have a date of birth between 01 May 2002 and 30 Apr 2005, to have been born preterm at ≤ 35 weeks postmenstrual age, to have received at least three injections of SYNAGIS during their first RSV season with injections given at monthly intervals no less than 21 days and no more than 35 days apart (SYNAGIS group only), and to have had a life expectancy > 6 months. Subjects could not have had medical intervention for bronchopulmonary dysplasia/ chronic lung disease within 6 months of entering the Screening Period, mechanical ventilation (including continuous positive airway pressure), or renal impairment, hepatic dysfunction, or seizure disorder. Subjects were not to have received SYNAGIS in more than one RSV season.

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

No study drug was administered.

Duration of Treatment:

No study drug was administered.

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

No study drug was administered.

Criteria for Evaluation

Efficacy:

The primary and sole efficacy endpoint was the incidence of respiratory hospitalizations during the second RSV season.

Safety:

Safety was assessed by the incidence of SAEs.

Statistical Methods

The primary efficacy analysis set (N=1884) included:

- All Included Study M02-489 subjects were those matched pairs of subjects in which one of the pair had an RSV+ hospitalization during the second RSV season and those matched pairs of subjects in which both subjects were followed for at least 120 days of the second RSV season, with neither having an RSV+ hospitalization, and neither having a respiratory-related hospitalization without RSV testing.
- All Included Study W00-353 subjects who were in the SYNAGIS group or in the Control group with no prior RSV hospitalization. These subjects must have had an RSV+ hospitalization or must have had no RSV+ hospitalization but were followed for at least 120 days in the second RSV season and had no respiratory-related hospitalization without RSV testing.
- All enrolled subjects from Study W99-311.

The primary SAE analysis set (N=1888) included all subjects in the primary efficacy analysis set plus 44 subjects excluded from the primary efficacy analysis set due to insufficient follow-up and/or respiratory-related hospitalization without RSV testing.

Efficacy:

The primary endpoint was the incidence of hospitalization with a positive RSV test (*i.e.*, RSV+ hospitalization) during the second RSV season following SYNAGIS treatment in the primary efficacy analysis set (combined data from Studies M02-489, W00-353, and W99-311). The primary analysis of the incidence of RSV hospitalization was a non-inferiority test based on a one-sided 97.5% exact confidence interval for the difference in RSV hospitalization rate between SYNAGIS and the risk-matched Control group. Non-inferiority was met if the bound of the upper 97.5% confidence interval for SYNAGIS minus Control in the RSV+ hospitalization rate was less than 0.03 (*i.e.*, 3% difference in incidence). Two sensitivity analyses of the primary efficacy endpoint were conducted. Each sensitivity analysis included all subjects included in the primary efficacy analysis set, plus hospitalized (respiratory-related) subjects without RSV testing in Studies M02-489 and W00-353. In one sensitivity analysis, subjects from Studies M02-489 and W00-353 without RSV testing were considered to have RSV+ hospitalizations, and in the other, they were considered to have had RSV- hospitalizations. Estimates of the relative risk and odds ratio were provided with 95% confidence intervals for each of the three analyses (primary and two sensitivity analyses). Descriptive summaries of RSV hospitalization rates for each group were provided by matching group, geographic region, potential Baseline predictive factors, study, and year.

Safety:

The incidence of SAEs was summarized by group. SAEs from Studies M02-489 and W00-353 were coded with Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) V for analysis. SAEs from Study W99-311 were coded using a World Health Organization (WHO) dictionary.

Summary/Conclusions

Efficacy Results:

Efficacy results demonstrate that children who received SYNAGIS were not at an increased risk for hospitalization with severe RSV in the subsequent respiratory season: No statistically significant difference in the incidence of RSV+ hospitalization was observed between the SYNAGIS (2.06%) and Control (1.26%) groups. The upper bound of the one-sided 97.5% confidence interval for the difference in event rates was 1.96% using the normal approximation to the binomial distribution and 2.77% using an exact method. Thus, the SYNAGIS group demonstrated non-inferiority to the control group with respect to the rate of RSV+ hospitalization.

Two sensitivity analyses of the primary efficacy endpoint were conducted. Each sensitivity analysis included all subjects included in the primary efficacy analysis set, plus hospitalized (respiratory related) subjects without RSV testing in Studies M02-489 and W00-353. In one sensitivity analysis, subjects from Studies M02-489 and W00-353 without RSV testing were considered to have had RSV+ hospitalizations, and in the other, they were considered to have had RSV- hospitalizations. Results of both sensitivity analyses were consistent with those of the primary analysis: The upper bounds of the one-sided 97.5% confidence intervals (exact and asymptotic) were below 3%, and thus, the SYNAGIS group demonstrated non-inferiority relative to the Control group.

The results of subgroup analyses were consistent with the results of the primary analysis; rates of RSV+ hospitalization in each subgroup were generally comparable across treatment groups. Rates of RSV+ hospitalization ranged from 0 to 4.71% in subgroups of SYNAGIS-treated subjects, and from 0 to 4.76% in subgroups of control subjects.

Tabular efficacy data:

Primary Analysis[a]	**SYNAGIS N=972**	**Control N=872**	**p-value**[b]
Number of Subjects Hospitalized, n (%)	20 (2.06)	11 (1.26)	0.207
Difference in rates (SYNAGIS minus Control)			
Difference, %	0.80		
Upper 97.5% Exact confidence bound (%)[c]	2.77		
Upper 97.5% asymptotic confidence bound (%)[d]	1.96		
Relative Risk (95% CI[e])	1.63 (0.79, 3.38)		
Odds Ratio (95% CI[e])	1.64 (0.78, 3.45)		

Missing RSV tests counted as RSV+[f]			
	SYNAGIS N=991	**Control N=890**	**p-value[b]**
Number of Subjects Hospitalized, n (%)	30 (3.03)	22 (2.47)	0.485
Difference in rates (SYNAGIS minus Control)			
Difference, %	0.56		
Upper 97.5% exact confidence bound (%)[c]	2.82		
Upper 97.5% asymptotic confidence bound (%)[d]	2.03		
Relative Risk (95% CI)[d]	1.22 (0.71, 2.11)		
Odds Ratio (95% CI)[d]	1.23 (0.71, 2.15)		
Missing RSV tests counted as RSV-[g]			
	SYNAGIS N=990[h]	**Control N=889[h]**	**p-value[b]**
Number of Subjects Hospitalized, n (%)	20 (2.02)	11 (1.24)	0.207
Difference in rates (SYNAGIS minus Control)			
Upper 97.5% exact confidence bound (%)[c]	0.78		
Upper 97.5% asymptotic confidence bound (%)[d]	1.92		
Relative Risk (95% CI[e])	1.63 (0.79, 3.39)		
Odds Ratio (95% CI[e])	1.65 (0.78, 3.45)		

a. This analysis excludes subjects from Studies M02-489 and W00-353 who had no RSV+ hospitalization but had ≥ 1 hospitalization without RSV testing. Hospitalized subjects from Study W99-311 who did not have RSV testing were counted as RSV+.

b. The p-value is from Fisher's Exact test.

c. One-sided upper 97.5% exact confidence bound.

d. One-sided upper 97.5% confidence bound based on the normal approximation.

e. Two-sided 95% CI based on the normal approximation.

f. Subjects from Studies M02-489 and W00-353 who had ≥ 1 hospitalization without RSV testing were counted as RSV+. Hospitalized subjects from Study W99-311 without RSV testing were counted as RSV+.

g. Subjects from Studies M02-489 and W00-353 who had no RSV+ hospitalization but had ≥ 1 hospitalization without RSV testing were counted as RSV-. Hospitalized subjects from Study W99−311 without RSV testing were counted as RSV+.

h. Study M02-489 SYNAGIS Subject [redacted] was excluded from the primary analysis due to lack of RSV testing; his matched Control Subject [redacted] was excluded due to insufficient follow-up. Both subjects were included in the first sensitivity analysis because subjects with RSV+ hospitalizations (and their matched pairs) were automatically included even if follow-up was insufficient. They were excluded from the second sensitivity analysis because Control Subject [redacted] had insufficient follow-up.

redacted information 30Jul2014

Safety Results:

No safety signals were detected in infants who had previously received SYNAGIS prophylaxis in their first RSV season.

Two deaths were reported during Study M02-489; however, both children had not received SYNAGIS.

For the primary SAE analysis set, a statistically significantly greater proportion of subjects from the Control group reported an SAE during the study compared to the SYNAGIS group (10.9% and 7.8%, respectively; $p \leq 0.050$).

By body system, SAEs were most frequently respiratory in nature. Respiratory system was the only body system for which greater than 5% of subjects in either group reported at least one event. The digestive system was the only body system for which a statistically significant difference ($p \leq 0.050$) was observed between groups (0.8% SYNAGIS and 3.1% Control). By COSTART term, SAEs with the highest incidence were pneumonia, bronchiolitis, and bronchitis. A statistically significantly greater proportion of SYNAGIS subjects reported bronchiolitis compared to Control subjects (1.9% *vs.* 0.7%, respectively; $p \leq 0.050$). A statistically significantly greater proportion of Control subjects reported bronchitis compared to SYNAGIS subjects (2.8% *vs.* 1.0%, respectively; $p \leq 0.050$).

The most frequently reported (≥ 3 subjects in any group) SAEs with onset during the second RSV season by COSTART term are as follows:

	SYNAGIS N=995	Control N=893	p-value[a]
COSTART Term	**n (%)**		
Any	78 (7.8)	97 (10.9)	≤ 0.050
Accidental injury	4 (0.4)	3 (0.3)	-
Fever	3 (0.3)	3 (0.3)	-
Hernia	1 (0.1)	3 (0.3)	-
Infection	4 (0.4)	5 (0.6)	-
Reaction unevaluable	3 (0.3)	1 (0.1)	-
Diarrhea	1 (0.1)	4 (0.4)	-
Enterocolitis	1 (0.1)	4 (0.4)	-
Gastroenteritis	6 (0.6)	13 (1.5)	-
Convulsion	3 (0.3)	4 (0.4)	-
Asthma	6 (0.6)	4 (0.4)	-
Bronchiolitis	19 (1.9)	6 (0.7)	≤ 0.050
Bronchitis	10 (1.0)	25 (2.8)	≤ 0.050
Laryngitis	3 (0.3)	1 (0.1)	-
Pharyngitis	2 (0.2)	6 (0.7)	-
Pneumonia	20 (2.0)	17 (1.9)	-
Otitis media	2 (0.2)	4 (0.4)	-
Pyelonephritis	0	3 (0.3)	-

a. Fisher's Exact Test

Note: SAEs were grouped into COSTART terms according to COSTART Dictionary V (Studies M02−489 and W00−353) and a WHO Dictionary (Study W99−311).

All SAEs reported during Study M02-489 were considered by the Investigator to be not related or probably not related to study drug. Vital signs measurements and physical examination results were unremarkable.

Conclusions:

Data from Study M02-489 successfully provided, in conjunction with data from Studies W99-311 and W00-353, further documentation of the safety of SYNAGIS treatment over a second respiratory season:

In Study M02-489 no safety signals were detected in infants previously treated with SYNAGIS. More specifically, the results of Study M02-489 demonstrate that infants who received SYNAGIS during their first year of life are not at an increased risk for hospitalization with severe RSV in the subsequent respiratory season.

Report Date: 15 December 2005