2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: SYNAGIS (Finished Product)	**Volume:** **Page:**	
Name of Active Ingredient: Palivizumab (genetical recombination)		

Title of Study:
Multi-center, Open-label, Uncontrolled Clinical Study of Palivizumab in Japanese Newborns, Infants and Young Children at the Age of 24 Months or Less with Immunocompromised Medical Conditions

Investigator: Investigator information is on file ▮▮▮▮ redacted information 30Jul2014

Study Sites: 6 sites in Japan

Publications: There were no publications based on this study.

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 22 August 2011 Last Subject Last Visit: 25 April 2012	

Objectives:

The primary objective of this study was to evaluate safety, efficacy and pharmacokinetics (PK) of palivizumab in children at the age of 24 months or less with immunocompromised medical conditions. The secondary objective of this study was to evaluate the trough serum concentration (C_{trough}) of palivizumab obtained from Japanese subjects with immunocompromised medical conditions, compared to the C_{trough} of palivizumab numerically with available previous data in Japanese premature newborns and infants, and children with bronchopulmonary dysplasia (BPD), and children with hemodynamically significant congenital heart disease (CHD).

Methodology:

This study was a phase 3, multi-center, open-label, uncontrolled, multiple-dose study to evaluate safety, efficacy and PK of palivizumab in newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions. Approximately twenty subjects were to be enrolled into this study. The study period consisted of a screening period, an administration period of the study drug, and a safety follow-up period after the subject either completed or prematurely discontinued from the study.

The subjects were to be enrolled into this study after obtaining the written informed consent to participate in this study from subject's parents or legal guardians. The time from enrollment to the initial administration of the study drug was defined as the screening period. The investigator was to judge which subjects would be eligible for entry into the study during the screening period and select eligible subjects as study subjects as defined by the inclusion and exclusion criteria. Approximately four weeks were scheduled for the screening period. Following the screening period, the selected subjects were to

receive a minimum of 4 doses up to a maximum of 7 doses of the study drug palivizumab at 15 mg/kg of body weight by intramuscular injection every 30 days during the 2011 - 2012 respiratory syncytial virus (RSV) season.

Blood samples for evaluation of palivizumab C_{trough} were to be collected at Screening, Day 31 and Day 121, or 30 days after the last dose of the study drug, if the subject was discontinued prior to the 5th administration of the study drug. Evaluation of efficacy with regard to subject's hospitalization associated with RSV infection, included requirement for oxygen supplementation, mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, other mechanical respiratory support or Intensive Care Unit (ICU) admission for RSV hospitalizations was to be performed from the initial dose to 30 days after the last dose of the study drug. Safety was to be assessed at Screening, Day 1, 31, 61, 91 and 121 or at the early termination (ET) visit, and at Day 151, 181, or 211 if a 5th, 6th or 7th administration of the study drug was given, respectively. The primary endpoints of this study were to be the serum trough concentrations of palivizumab obtained 30 days after the initial administration and 30 days after the 4th administration of the study drug. The subjects who completed the study or who prematurely discontinued from the study were to have a 100-day follow-up after the last administration of the study drug to evaluate adverse events (AEs).

Number of Subjects (Planned and Analyzed):

Planned: 20; Enrolled: 30; Treated: 28;

All 28 subjects treated with study drug were included in "full analysis set" (FAS), which was used for efficacy, safety and pharmacokinetic evaluation.

Diagnosis and Main Criteria for Inclusion:

Japanese subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible for study participation.

Inclusion Criteria:

1. Availability of parent or legal guardian who was capable and willing to give written informed consent for his/her newborn, infant or young child to participate in this study.

2. Japanese newborn, infant or young child must have been 24 months of age or less at the start of study drug administration (i.e., must not have passed his/her second birthday).

3. The subject must have met at least one of the following immunocompromised medical conditions (from [a] to [h]), and must be considered by the investigator to be a suitable candidate to receive prophylactic treatment of palivizumab:

    [a] Subject had been diagnosed with combined immunodeficiency (severe combined immunodeficiency, X-linked hyper-immunoglobulin M (IgM) syndrome, etc.), antibody deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndrome, etc.) or other immunodeficiency (Wiskott-Aldrich syndrome, etc.) at the time of informed consent,

    [b] Subject had been diagnosed with human immunodeficiency virus (HIV) infection at the time of informed consent,

    [c] Subject had been diagnosed with Down syndrome* without a current hemodynamically significant CHD at the time of informed consent,

    [d] Subject had a history of post organ transplantation at the time of informed consent,

[e] Subject had a history of post bone marrow transplantation at the time of informed consent,

[f] Subject was receiving immunosuppressive chemotherapy at the start of study drug administration,

[g] Subject was receiving systemic high dose corticosteroid therapy (prednisone equivalents ≥ 0.5 mg/kg/every other day, other than inhaler or topical use) at the start of study drug administration, or

[h] Subject was receiving other immunosuppressive therapy (azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc.) at the start of study drug administration.

*: The subject must have had an experience with persistent respiratory symptom or regular outpatient treatment due to respiratory tract infection prior to current RSV season.

Exclusion Criteria:

1. Subject who met any of the palivizumab indications already approved in Japan.

    - Subject born at 28 weeks of gestation or less and who is age of 12 months or less at the start of study drug administration.

    - Subject born at 29 - 35 weeks of gestation and who is age of 6 months or less at the start of study drug administration.

    - Subject is age of 24 months or less with a history of BPD requiring medical management within the 6 months prior to the study drug administration.

    - Subject is age of 24 months or less with a current hemodynamically significant CHD at the start of study drug administration.

2. Subject required oxygen supplementation, mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure or other mechanical respiratory or cardiac support at Screening.

3. Subject had a current active infection including RSV infection at Screening.

4. Subject had a serious concurrent medical condition (hepatic dysfunction, persistent seizure disorder, etc.), except those resulting in an immune deficiency condition or renal failure.

5. Subject had received palivizumab prior to the study drug administration.

6. Subject had received any other investigational agents in the past 3 months or within 5 half lives prior to the investigational drug administration (whichever was longer).

7. Subject had a history of an allergic reaction or hypersensitivity to constituents of the study drug.

8. Subject had a history of serious adverse reactions or serious allergic reaction to immunoglobulin products or has a history of hypersensitivity to immunoglobulin products, blood products, or other foreign proteins.

9. Subject whose remaining days of life were expected to be less than one year at the time of informed consent.

10. It would have been impossible to collect blood as scheduled from the subject.

11. Subject was considered by the investigator, for any reason, to be an unsuitable candidate for the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:	
Investigational Product:	palivizumab
Dose:	15 mg/kg at 30-day interval, at least 4 injections up to a maximum of 7 injections as appropriate for prophylaxis of RSV infection
Mode of Administration:	Intramuscular injection
Batch Number/Bulk Lot Number:	▮▮▮▮▮▮▮

Duration of Treatment: `redacted information 30Jul2014`

September 2011 - March 2012

The subject enrollment period was to begin 1 September 2011 and end 30 November 2011.

At least 4 injections up to a maximum of 7 injections as appropriate for prophylaxis of RSV infection.

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

Not applicable

Criteria for Evaluation

Primary endpoint

Serum trough concentrations of palivizumab obtained 30 days after the initial administration and 30 days after the 4th administration (Day 121) of the study drug.

Efficacy:

Rate of hospitalization due to RSV infection from initial administration to 30 days after final administration of the study drug.

Safety:

Adverse events, vital signs, body weight and laboratory data.

Statistical Methods

Pharmacokinetic:

Trough serum concentrations of palivizumab were to be summarized at each time point using descriptive statistics including number of observations/subjects (n), number of non-missing observations (nnmiss), arithmetic mean (mean), median, standard deviation (SD), coefficient of variation (CV), minimum (Min) and maximum (Max), and 95% confidence interval (95% CI) of the mean.

Efficacy:

Frequency (n) and percentages (%) of subjects who needed hospitalization due to RSV infection were to be calculated from the initial dose to 30 days after the last dose of the study drug. The 95% CI was to be also calculated.

Safety:

1. The number and percentages of subjects experiencing treatment-emergent adverse event were to be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). In addition, a summary of adverse events by severity and relationship to the study drug was to be presented. Summary of serious and severe treatment-emergent adverse events, deaths, and adverse events leading to discontinuation of the study were also to be provided. Pre-treatment serious adverse events were to be summarized as well.

2. Visit values and changes from baseline to each scheduled visit and for the endpoint value in laboratory variables, vital signs variables, and body weight were to be summarized with the descriptive statistics specified for the quantitative/continuous variables.

Summary/Conclusions

A total of 30 subjects were enrolled and 28 subjects were treated with study drug. All 28 subjects treated with study drug were included in FAS, which was used for efficacy, safety and PK evaluation.

Efficacy Results:

No subjects experienced a confirmed RSV hospitalization after the initial dose to 30 days after the last dose of the study drug. As such, the incidence of RSV hospitalization was 0.0% (95% CI: 0.0-12.3) in the study. As such, no subject required any treatments for RSV infection after the initial dose to 30 days after the last dose of the study drug, so the proportion of subjects who required treatment was 0.0% (95% CI: 0.0-12.3) in this study. Therefore, the prophylactic use of palivizumab was considered to be effective in Japanese newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions in preventing serious disease due to RSV infection.

Pharmacokinetic Results:

Summary of serum Palivizumab trough concentrations (µg/mL)

| Treatment | Mean ± SD (Min − Max), N_{nmiss} | | |
	Day 1 (Screening)	Day 31	Day 121
Palivizumab, 15 mg/kg, intramuscular injection, every 30 days	0 ± 0 (0 − 0), 28	59.0 ± 12.9 (36.6 − 84.1), 28	91.8 ± 40.6 (29.8− 181), 26

Summary of serum palivizumab trough concentrations in Japanese pediatric subjects with immunocompromised medical conditions (Study M12-420), hemodynamically significant CHD (Study MED493-301/M03-637) and Japanese premature newborns or pediatric subjects with BPD (Study J-MED-99-002)

| Time (Day) | Serum Palivizumab Trough Concentrations (µg/mL) | | |
| | Mean ± SD (N_{nmiss}) | | |
	Japanese Pediatric Subjects with Immunocompromised Medical Conditions	Japanese Pediatric Subjects with Hemodynamically Significant CHD	Japanese Premature Newborns or Pediatric Subjects with BPD
30 days after 1st dose	59.0 ± 12.9 (28)	57.2 ± 11.7 (67)	50.5 ± 17.5 (31)
30 days after 2nd dose	NA	NA	76.8 ± 17.6 (31)
30 days after 4th dose	91.8 ± 40.6 (26)	90.2 ± 23.7 (67)	NA

N_{nmiss} = number of non-missing observations

Safety Results:

Of the 28 subjects treated with study drug, all subjects received at least 2 doses of study drug, 27 subjects (96.4%) received at least 4 doses and 16 subjects (57.1%) received 7 doses. Twenty-seven subjects (96.4%) experienced at least one AE during treatment through 100 days following the last dose of the study drug.

The most frequently reported AEs were upper respiratory tract infection (10 subjects, 35.7%), gastroenteritis and eczema (9 subjects each, 32.1%), and influenza (6 subjects, 21.4%). These AEs reported in the study are commonly observed in newborns, infants and young children in health or immunocompromised medical conditions.

The majority of AEs were assessed as mild or moderate in severity by the investigator. Two subjects (7.1%) experienced at least one severe AE during the study. Subject ▮▮▮ experienced encephalopathy, and Subject ▮▮▮ experienced gastrointestinal perforation, infectious peritonitis and duodenal stenosis reported as severe AEs. `redacted information 30Jul2014`

No AEs were assessed as possibly or probably related to study drug by the investigator. Seven subjects (25.0%) experienced AEs assessed as probably not related to study drug during the study. Nasopharyngitis was the only AE assessed as probably not related to study drug that was reported in more than 1 subject (2 subjects).

Thirteen SAEs were reported in 7 subjects (25.0%) in the study. The most frequently reported SAEs were gastroenteritis (3 subjects, 10.7%) and bronchitis (2 subjects, 7.1%). Of the 13 SAEs, 9 and 4 events were assessed as moderate and severe, respectively. Twelve events were assessed as not related to study drug, while 1 event (encephalopathy) was assessed as probably not related to study drug. Subject ▮▮▮ who experienced the SAE of encephalopathy, also experienced an SAE of gastroenteritis during the study. The encephalopathy was assessed as a persistent disability that was severe and probably not related to study drug; and the subject had not recovered from the event by the end of the study. Due to the SAE of encephalopathy, the subject prematurely discontinued the study after the 4th dose of study drug. `redacted information 30Jul2014`

Eight subjects experienced 11 AEs suspected to be RSV infection in the study. Of the 11 events, 4 events resulted in hospitalization (Subject ▮▮▮ bronchitis, ▮▮▮ pneumonia, ▮▮▮ croup infectious and pneumonia bacterial). In these 4 events, RSV antigen detection tests were performed and a negative result was obtained in each case. `redacted information 30Jul2014`

There were no deaths, AEs leading to death or AEs assessed as possibly or probably related to study drug by the investigator during the study.

None of the mean changes from baseline in variables of hematology, blood chemistry, urinalysis qualitative analysis and vital sign were considered clinically important throughout the study.

In summary, the prophylactic use of palivizumab was generally safe and well tolerated in Japanese newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions in this study.

Conclusions:

This study was designed as a multi-center, open-label, uncontrolled clinical study of palivizumab in Japanese newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions.

In Japanese pediatric subjects with immunocompromised medical conditions, the mean ± SD serum palivizumab trough concentrations at Day 31 (30 days after the 1st dose) and Day 121 (30 days after the 4th dose) were 59.0 ± 12.9 µg/mL and 91.8 ± 40.6 µg/mL, respectively, following a 15 mg/kg intramuscular injection every 30 days.

In the efficacy evaluation, no subjects experienced a confirmed RSV hospitalization after the initial dose to 30 days after the last dose of the study drug in the study. Likewise, no subjects required additional

treatment for RSV infection after the initial dose to 30 days after the last dose of the study drug, since there were no RSV hospitalizations.

In the safety evaluation, the prophylactic use of palivizumab was generally safe and well tolerated in this study.

In conclusion, the prophylactic use of palivizumab was considered to be effective and safe in Japanese newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions in preventing serious disease due to RSV infection.   Serum palivizumab trough concentrations in Japanese pediatric subjects with immunocompromised medical conditions were comparable to those in Japanese premature with hemodynamically significant CHD and Japanese premature newborns or pediatric subjects with BPD.

Date of Report: 11Oct2012