21 November 2013
EMA/CHMP/780068/2013
Committee for Medicinal Products for Human Use (CHMP)

Synagis

(Palivizumab)

Procedure no. EMA/H/C/000257/P46/036

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Introduction

On July 30, 2013, the MAH submitted seven completed paediatric studies for palivizumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview for each study has also been provided.

The MAH states that four of the submitted paediatric studies (M12-420, W10-664, MI-CP118, MI-CP127) do not influence the benefit risk for palivizumab and that no consequential regulatory action is required.

Studies MI-CP116, MI-CP110 and MI-CP124 will be submitted as supportive clinical experience in an extension application consisting of the full relevant data package to register the solution for injection formulation in the EU; expected to be submitted by October 2013.

Scientific discussion

Information on the development program

The MAH stated that:

Study M12-420, 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;

Study W10-664, A Prospective, Multicenter, Open-label, Non-comparative Study of Safety and Efficacy of Palivizumab (Synagis) in Children at High Risk of Severe Respiratory Syncytial Virus Infection in the Russian Federation;

Study MI-CP118, A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524, Numax), a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), after Dosing for a Second Season in Children who Previously Received MEDI-524 in Protocol MI-CP104;

Study MI-CP127, A Phase 2, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524), a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), and Palivizumab When Administered in the Same Season;

Study MI-CP116, A Phase IV, Randomized, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilized Formulations of Palivizumab (MEDI-493, Synagis) in Children at High Risk for the Development of Serious RSV Disease;

Study MI-CP110, A Pivotal Phase 3 study of MEDI-524, an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prophylaxis of Serious RSV disease in High-risk Children, and

Study MI-CP124, A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody against Respiratory Syncytial Virus (RSV), in Children with Hemodynamically Significant Congenital Heart Disease are stand-alone studies.

The MAH stated that none of the studies are part of a clinical development program. Studies MI-

CP116, MI-CP110 and MI-CP124 will be submitted as supportive clinical experience in an extension application consisting of the full relevant data package which is expected to be submitted by October 2013.

Of note, motavizumab (MEDI-524, Numax) development has been discontinued.

Information on the pharmaceutical formulation used in the studies

Palivizumab is a humanized monoclonal antibody (IgG1κ) specific for the fusion protein (F-protein) of RSV that has potent neutralizing and fusion-inhibitory activity against a broad range of RSV isolates. Based on clinical studies in children with chronic lung disease the product was licensed in the US in 1998 and in the EU in 1999. Further studies have subsequently been conducted in different patient groups and the indications currently approved are

"SYNAGIS is indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease:

- Children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season.
- Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months.
- Children less than 2 years of age and with haemodynamically significant congenital heart disease."

The pharmaceutical formulations used in the studies were:

Palivizumab was provided in sterile vials containing 100 mg of palivizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine.

Lyophilized palivizumab was provided in sterile vials containing 100 mg

Motavizumab was provided in sterile vials containing 100 mg of motavizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidinehydrochloride. As mentioned above, the development of motavizumab has been discontinued.

Clinical aspects

1. Introduction

The MAH submitted final reports for:

- Study M12-420, 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;
- Study W10-664, A Prospective, Multicenter, Open-label, Non-comparative Study of Safety and Efficacy of Palivizumab (Synagis) in Children at High Risk of Severe Respiratory Syncytial Virus Infection in the Russian Federation;
- Study MI-CP118, A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524, Numax), a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), after Dosing for a Second Season in Children who Previously Received MEDI-524 in Protocol MI-CP104;
- Study MI-CP127, A Phase 2, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524), a Humanized Enhanced Potency Monoclonal

Antibody Against Respiratory Syncytial Virus (RSV), and Palivizumab When Administered in the Same Season;

- Study MI-CP116, A Phase IV, Randomized, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilized Formulations of Palivizumab (MEDI-493, Synagis®) in Children at High Risk for the Development of Serious RSV Disease;
- Study MI-CP110, A Pivotal Phase 3 study of MEDI-524 (Numax™), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prophylaxis of Serious RSV disease in High-risk Children, and
- Study MI-CP124, A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody against Respiratory Syncytial Virus (RSV), in Children with Hemodynamically Significant Congenital Heart Disease

2. Clinical studies

M12-420. 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

Description

Methods

- Objectives

The primary objective 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 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).

- Study design

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. 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. 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 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).

- Study population /Sample size

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.

Approximately twenty subjects were to be enrolled into this study.

- Treatments

Palivizumab 15 mg/kg IM at 30-day interval, at least 4 injections up to a maximum of 7 injections as appropriate for prophylaxis of RSV infection

- Outcomes/endpoints

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.

Results

- Recruitment/ Number analysed

A total of 30 subjects were enrolled at 6 sites in Japan. The 28 subjects treated with study drug were included in FAS, which was used for efficacy, safety and PK evaluation.

- Pharmacokinetic Results

Summary of serum Palivizumab trough concentrations (µg/mL)

	Mean ± SD (Min – Max), N_{nmiss}		
Treatment	**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)

	Serum Palivizumab Trough Concentrations (µg/mL)		
	Mean ± SD (N_{nmiss})		
Time (Day)	**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

- 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.

- 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. One subject experienced encephalopathy and another experienced gastrointestinal perforation, infectious peritonitis and duodenal stenosis reported as severe AEs.

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. One 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.

Eight subjects experienced 11 AEs suspected to be RSV infection in the study. Of the 11 events, 4 events resulted in hospitalization (One subject: bronchitis, one subject: pneumonia, one subject: croup infectious and pneumonia bacterial). In these 4 events, RSV antigen detection tests were performed and a negative result was obtained in each case.

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.

CHMP's comment:

This small study was requested by the Japanese Pharmaceutical and Medical Devices Agency and conducted in 2011-2012. Children with immunocompromised medical conditions are outside of the patient populations included in the current indication for prophylaxis in the EU. None of the 28 children experienced a confirmed RSV hospitalization after the initial dose to 30 days after the last dose of the study drug in the study; and no subjects required additional treatment for RSV infection after the initial dose to 30 days after the last dose of the study drug. Palivizumab was generally safe and well tolerated. Furthermore, serum palivizumab trough concentrations in these children with immunocompromised medical conditions were comparable to those in Japanese premature with hemodynamically significant CHD and Japanese premature newborns or pediatric subjects with BPD.

W10-664. 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.

Description

Methods

- Objective(s)

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.

- Study design

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.

- Study population /Sample size

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).

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.

- Treatments

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 15 mg/kg was to be administered intramuscular 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.

- Outcomes/endpoints

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.

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.

Results

- Recruitment/ Number analysed

As planned, 100 subjects were enrolled at 19 centers in the Russian Federation 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).

- Baseline data

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).

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.

CHMP's comments:

The liquid formulation of palivizumab, which is not approved in Europe, was used in this small open Russian study conducted 2009/2010. 98 children fulfilling the approved indications for Synagis were enrolled (33% were preterm infants born ≤ 35 weeks GA and ≤ 6 months of age at enrollment, 46% were infant's ≤ 24 months of age at enrollment with a diagnosis of BPD, and 30% infants ≤ 24 months at enrollment with HSCHD). The efficacy and safety was in accordance with results of other studies.

MI-CP118 - A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), after Dosing for a Second Season in Children who Previously Received MEDI-524 in Protocol MI-CP104

Description

Methods

- Objectives

The primary objective of this study was to determine the effect on immune reactivity to MEDI-524 of monthly intramuscular (IM) doses of MEDI-524 administered for a second season in children who previously received MEDI-524 in protocol MI-CP104.

The secondary objectives of this study were to:

1. Describe the safety and tolerability of MEDI-524 administered for a second season
2. Describe the serum concentration of MEDI-524 administered for a second season

- Study design

A Phase 1/2, randomized, double-blind study in which MEDI-524 or palivizumab was administered to children who previously participated in MI-CP104. Patients were randomized 1:1 to receive MEDI-524

or palivizumab at 15 mg/kg by IM injection every 30 days for a total of 4-5 injections during the 2004-05 RSV season subsequent to the season in which they were participants of MI-CP104. All patients were evaluated prior to and 30 minutes after each injection of study drug with 2 follow-up evaluations, one at 30 days and the other at 90-120 days after the last dose.

- Study population /Sample size

Children who received at least 3 doses of MEDI-524 in MI-CP104 were eligible for enrollment. Approximately 150 patients were planned for enrollment.

- Treatments

MEDI-524 or palivizumab at 15 mg/kg by IM injection every 30 days for a total of 4-5 injections during the 2004-05 RSV season subsequent to the season in which they were participants of MI-CP104.

- Outcomes/endpoints

Immunogenicity and Pharmacokinetics: Serum for measurement of anti-MEDI-524 antibodies and MEDI-524 concentrations was collected prior to the first, second and, if applicable, fifth doses of study drug, and at the 2 follow-up visits 30 and 90-120 days after the last dose.

Safety: Adverse events (AEs), serious adverse events (SAEs), and concomitant medications were collected from the period immediately following the first administration of study drug through Study Day 120 for patients who received 4 doses, and Study Day 150 for patients who received 5 doses of study drug. Blood was collected prior to the first, second and, if applicable, fifth doses of study drug, and at 30 days after the last dose for serum chemistry and complete blood count (CBC) evaluation.

- Statistical Methods

All tabular summaries were presented by treatment group. Categorical data were summarized by the number and percent of patients in each category. Continuous variables were summarized by descriptive statistics including mean, standard deviation, minimum, and maximum. No statistical tests were planned or conducted.

Results

- Recruitment/ Number analysed

136 were randomized (66 MEDI-524;70 palivizumab). All children received study drug and had follow-up for safety, and are therefore included in all summaries of safety and immunogenicity. Two patients, both in the MEDI-524 group, were excluded from the pharmacokinetics analyses subsequent to receiving an incorrect dose or missing a dose.

- Baseline data

The patients in this study were children (≤24 months of age) who previously participated in MI-CP104 and received at least 3 injections of MEDI-524 in that study. Baseline demographics were similar and balanced between the MEDI-524 and palivizumab groups. The study drugs were well-tolerated with a total of 131 (96.3%) children completing the study, 4 withdrew consent, and 1 was lost to follow-up. A total of 98% (64/66) of children assigned to the MEDI-524 group received 5 (82%) or 4 (16%) doses of study drug. One child in the MEDI-524 group was permanently discontinued from study drug, due to a serious adverse event (hypersensitivity).

- Immunogenicity

Anti-MEDI-524 binding activity responses (defined as a titer with a dilution of ≥1:10) were detected at baseline prior to second-season dosing in 2 (3.0%) patients in the MEDI-524 group, 1 of whom also had anti-MEDI-524 binding activity detected previously during participation in MI-CP104. However, no

anti-MEDI-524 binding activity responses were detected after dosing through study completion in any patient who received MEDI-524, including the 2 patients with anti-MEDI-524 binding activity detected at baseline prior to second-season dosing. Both patients achieved MEDI-524 serum trough drug levels through 90-120 days post final dose that were within the range of values seen in patients who had no anti-MEDI-524 binding activity detected pre-dose.

In a post hoc analysis, anti-palivizumab binding activity responses (defined as a titer with a dilution of ≥1:10) in patients who received palivizumab in this trial were not detected at any time point before or after dosing (through 90-120 days after final dose).

- Safety results

A total of 56 (84.8%) MEDI-524 patients and 62 (88.6%) palivizumab patients experienced at least 1 AE. The majority (96% MEDI-524; 99% palivizumab) of AEs were Level 1 or 2 in severity. The pattern and type of AEs were generally consistent with the underlying conditions in this pediatric age group, and the incidence was similar between the MEDI-524 and palivizumab treatment groups. Laboratory abnormalities in routine blood chemistry or hematology occurred infrequently and, for the most part, were mild in severity.

A total of 12 patients in each of the MEDI-524 (18.2%) and palivizumab (17.1%) groups experienced at least 1 AE considered to be related to study drug. The most common of these was injection site erythema (15.2% MEDI-524; 11.4% palivizumab); all the events were transient lasting 1-2 days, were judged to be Level 1 in severity, and appeared not to be associated with dose number. A total of 5 children (4[6.1%] MEDI-524; 1[1.4%] palivizumab) experienced 6 serious adverse events (SAEs); 5 were judged to be unrelated to study drug and 1 related SAE, an acute hypersensitivity event, occurred immediately following the third dose of MEDI-524 and resulted in discontinuation of further dosing.

Pharmacokinetics:

In children given repeat doses of 15 mg/kg MEDI-524 during a second RSV season, mean trough serum MEDI-524 concentrations rose throughout dosing as expected. The mean serum trough levels and ranges of MEDI-524 in MI-CP118 following the first and fourth dose [54.6 µg/mL (range: 16.5-87.2 µg/mL) and 86.2 µg/mL (range: 37.5-148 µg/mL), respectively] were similar to those achieved in the first season of dosing in MI-CP104 [50.2 µg/mL (range: 2.76-106 µg/mL) and 86.2 µg/mL (range: 0-194 µg/mL), respectively]. By 90-120 days post final dose, MEDI-524 levels in all patients were below 30 µg/mL.

CHMP's comments:

In this study children who received repeat doses of motavizumab in the RSV season 2004/2005, were randomized 1:1 to receive motavizumab or palivizumab during the following RSV season. The treatment was well tolerated. Anti-motavizumab binding activity was not detected during dosing through 90-120 days after the final dose in any patient who received motivuzumab for a second season, including 2 children who had anti-motavizumab binding activity detected prior to the start of second-season dosing. As indicated previously, the development of motavizumab has been discontinued.

MI-CP127. A Phase 2, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524), a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), and Palivizumab When Administered in the Same Season.

Description

Methods

- Objectives

The primary objective of this study was to evaluate the safety and tolerability of motavizumab and palivizumab when administered during the same RSV season.

The secondary objectives of this study were:

1. To describe the immunogenicity of motavizumab and palivizumab when administered during the same season
2. To describe the serum concentrations of motavizumab and palivizumab when administered during the same season

- Study design

This was a Phase 2, randomized, double-blind study in which motavizumab and palivizumab were administered to high-risk children during the same RSV season. It was anticipated that approximately 240 children (80 in each group) would be enrolled from the southern hemisphere during the upcoming RSV season (2006). Children were randomized into one of three regimens in a 1:1:1 ratio; the first group received 2 doses of motavizumab followed by 3 doses of palivizumab; the second group received 2 doses of palivizumab followed by 3 doses of motavizumab; and the third group received 5 doses of motavizumab. Motavizumab or palivizumab were administered at 15 mg/kg by IM injection every 30 days, for a total of 5 injections.

Children were evaluated just prior to each injection of study drug, at Study Day 150, and 120-150 days after the last dose. Monitoring for adverse events and serious adverse events occurred through Study Day 150. Blood was collected on Study Day 0 (prior to the first dose), prior to the third dose (Study Day 60), and on Study Day 150 for anti-motavizumab and anti-palivizumab antibody, serum levels of motavizumab and palivizumab, and serum chemistry, with an additional blood sample taken 120-150 days after the last dose for anti-motavizumab and antipalivizumab antibody and serum levels of motavizumab and palivizumab.

- Study population /Sample size

Children at high risk for RSV infection. 240 children planned (80 in each group).

- Treatments

Test product: Motavizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of motavizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidinehydrochloride.

Reference product: Palivizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of palivizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine.

One dose motavizumab or palivizumab on Study Days 0, 30, 60, 90, and 120 for a total of 5 injections.

- Outcomes/endpoints

Safety: Adverse events (AEs), serious adverse events (SAEs), and concomitant medications were collected from the period immediately following the first administration of study drug through Study Day 150. Blood for serum chemistry evaluation was collected prior to study drug administration on

Study Days 0, 60, 150, and, for patients who discontinued prematurely prior to Study Day 150, the final visit.

Immunogenicity and Pharmacokinetics: Serum for measurement of anti-motavizumab and anti-palivizumab antibodies and motavizumab and palivizumab serum concentrations was collected prior to study drug administration on Study Days 0 and 60, on Study Day 150, 120-150 days post final dose, and, for patients who discontinued prematurely, on the final visit.

- Statistical Methods

All tabular summaries were presented by treatment group. Categorical data were summarized by the number and percent of patients in each category. Continuous variables were summarized by descriptive statistics including mean, standard deviation, minimum, and maximum.

Results

- Recruitment/ Number analysed

A total of 18 investigators at 7 Chilean sites, 6 Australian sites, and 5 New Zealand sites participated in the study. A total of 260 children (83, 2 doses motavizumab, 3 doses palivizumab; 84, 2 doses palivizumab, 3 doses motavizumab; 93, 5 doses motavizumab) were randomized into the study.

- Baseline data

Baseline demographics were similar and balanced among the 3 groups with the exception that 61% of patients in the mixed motavizumab/palivizumab group were male, compared to 51% and 52% in the mixed palivizumab/motavizumab and control motavizumab treatment groups, respectively.

- Efficacy results

N/A

- Safety results

Overall, the 3 treatment groups had similar rates of AEs (92.8% mixed motavizumab/palivizumab, 90.4% mixed palivizumab/motavizumab, 89.2% control motavizumab), with the majority of AEs Level 1 or 2 in severity. There were imbalances noted in Level 3 AEs and SAEs such that there were higher frequencies of these AEs in the mixed motavizumab/palivizumab treatment group than in the other 2 groups ((Level 3 AEs: 15.7% mixed motavizumab/palivizumab, 6.0% mixed palivizumab/motavizumab, 6.5% control motavizumab; SAEs: 22.9% mixed motavizumab/palivizumab, 8.4% mixed palivizumab/motavizumab, 11.8% control motavizumab). These increases were consistently observed both prior to dose 3 (ie, before the second of the 2 study drugs was administered) and post dose 3 in the mixed motavizumab/palivizumab treatment group suggesting a cause other than receipt of both study drugs. The increased frequency of SAEs in the mixed motavizumab/palivizumab treatment group in either time period was attributable to SAEs in the System Organ Class of Infections and Infestations with few RSV infections reported. A total of 3 related SAEs were reported in 2 children in the mixed motavizumab/palivizumab group after the receipt of motavizumab only (visual disturbance and erythema multiforme) and 1 child in the control motavizumab group (abnormal liver function test). Two deaths occurred on study, one subsequent to a SAE of sepsis and the second subsequent to a SAE of pneumonia. While both deaths occurred in the mixed motavizumab/palivizumab treatment group, both occurred after receipt of motavizumab only, and neither death was felt to be related to study drug.

Immunogenicity: Overall, immunogenicity in all treatment groups was low (anti-motavizumab antibody: 5.1% mixed motavizumab/palivizumab, 2.4% mixed palivizumab/motavizumab, 0.0%

control motavizumab; anti-palivizumab antibody: 5.1%, 2.4%, and 1.1%, respectively). A total of 13 patients (8 patients, mixed motavizumab/palivizumab; 4 patients, mixed palivizumab/motavizumab; 1 patient control motavizumab) had anti-palivizumab and/or antimotavizumab antibody at protocol-specified time points. In the majority of these patients with detectable antibody, antibody was detected at Study Day 150 and/or 120-150 days post final dose. Anti-motavizumab titers ranged from 1:10 to 1:1250. Anti-palivizumab titers ranged from 1:10 to 1:20. One patient who was in the mixed motavizumab/palivizumab group had an SAE of erythema multiforme 2 days after the second dose of motavizumab (Study Day 28) that was judged to be probably related to study drug; anti-motavizumab antibody with a titer of 1:50 was detected subsequently at Study Day 150.

No anti-motavizumab antibody was detected at any protocol-specified time point in any patient in the control motavizumab treatment group.

Pharmacokinetics: In the mixed motavizumab/palivizumab, mixed palivizumab/motavizumab, and control motavizumab groups, as expected, mean serum trough levels of motavizumab were highest on Study Day 60 (74.74 µg/mL), Study Day 150 (93.05 µg/mL), and Study Day 150 (105.8 µg/mL), respectively. Mean serum trough levels of palivizumab were highest at Study Day 150 (107.4 µg/mL) in the mixed motavizumab/palivizumab treatment group and at Study Day 60 (87.37 µg/mL) in the mixed palivizumab/motavizumab treatment group. A low level of serum palivizumab or motavizumab was detected among samples from patients who had not received palivizumab or motavizumab, most probably due to a low level of cross-reactivity between the assays for serum palivizumab and motavizumab.

CHMP's comments:

Agrees with the MAH who concludes that in this study with a limited number of subjects, dosing of motavizumab and palivizumab during the same RSV season in high-risk children was safe and well-tolerated. The total number of subjects with AEs was similar among the 3 treatment groups. There was a higher number of SAEs in the motavizumab/palivizumab group; however, this was due to the occurrence of more SAEs in the SOC of Infections and Infestations and was not judged to be due to either study drug alone or that particular sequence of administration. Immunogenicity was low, and mean serum trough concentrations of motavizumab and palivizumab were within the ranges expected. These findings suggest that both motavizumab and palivizumab can be safely administered in high-risk children during a single RSV season. As indicated previously, the development of motavizumab has been discontinued.

MI-CP116. A Phase IV, Randomized, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilized Formulations of Palivizumab (MEDI-493, Synagis) in Children at High Risk for the Development of Serious RSV Disease

Description

Methods

- Objective

The primary objective of this study was to assess the immunogenicity of the liquid formulation of palivizumab compared to the lyophilized formulation.

- Study design

This was a Phase 4, randomized, double-blind study to provide additional data to compare immunogenicity [reported as anti-drug antibody (ADA)] of the liquid and lyophilized formulations of palivizumab in children at high risk for serious RSV disease. Subjects were randomized 1:1 to receive

either 15 mg/kg palivizumab liquid or lyophilized formulation by intramuscular (IM) injection every 30 days for a total of 5 injections during the RSV season. Subjects were monitored through Study Day 150 for serious adverse events (SAEs). Serum palivizumab concentrations and anti-palivizumab antibody were measured at baseline prior to dosing, and again at one time point between Study Days 240 and 300 (4 to 6 months after the final dose of study drug).

- Study population /Sample size

The subjects were medically stable children with chronic lung disease (CLD) of prematurity who were ≤24 months of age at randomization, *or* children born prematurely [≤35 weeks gestational age (GA)] who were ≤6 months of age at randomization.

Approximately 400 subjects were planned for enrollment.

- Treatments

Test product: Palivizumab (Synagis), liquid formulation, provided in sterile vials containing 100 mg of palivizumab in 1 ml of sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidine and 1.6 mM glycine.

Reference product: Lyophilized palivizumab provided in sterile vials containing 100 mg of sterile lyophilized product that when formulated (before lyophilization) contains 25 mM histidine, 1.6 mM glycine, and 3% (w/v) mannitol at pH 6.0. Reconstitution with 1 ml of Sterile Water for Injection yields palivizumab at a concentration of 100 mg/ml.

Dose and duration of both formulations: 15 mg/kg IM every 30 days for a total of 5 injections during the RSV season.

- Outcomes/endpoints

Immunogenicity and Pharmacokinetics: Serum for measurement of anti-palivizumab antibodies and palivizumab concentrations from both formulations was collected at baseline prior to first dose, and again at one time point between Study Days 240 and 300 (actual, 112 to 203 days after the final dose of study drug).

Safety: Serious adverse events (SAEs) were collected from the period immediately following the first administration of study drug through Study Day 150.

- Statistical Methods

All tabular summaries were presented by treatment group. Categorical data were summarized by the number and percent of subjects in each category. Continuous variables are summarized by descriptive statistics including mean, standard deviation, minimum and maximum. No statistical tests were planned or conducted.

Results

- Recruitment/ Number analysed

417 were randomized into the study at 51 sites in the United States between 20 October 2005 and 28 December 2006. A total of 4 subjects randomized at one site (2 liquid palivizumab, 2 lyophilized palivizumab) received all 5 doses of study drug, per drug accountability records. However, despite attempts by the MAH to contact the site, no further information including the case report forms on these subjects could be obtained. These 4 subjects are therefore excluded from all data analyses. The remaining 413 subjects were randomized (211 liquid palivizumab; 202 lyophilized palivizumab) and followed. All 413 subjects received at least one dose of study drug and are included in all summaries of safety. There were 7 subjects excluded from the immunogenicity analyses: 6 subjects for having

received only one dose of study drug, and one subject for not having a blood sample collected at baseline or Study Day 240-300.

- Baseline data

Each subject participated during a single RSV season. Compliance with dosing and follow-up was good with 95.0% of lyophilized palivizumab subjects and 94.8% of liquid palivizumab subjects receiving all 5 doses of study drug, and 94.1% and 93.4% completing the study, respectively.

- Efficacy results

N/A

- Immunogenicity:

Anti-palivizumab antibodies were detected in one (0.5%) subject in the lyophilized palivizumab group (at 154 days post final dosing) and no subjects in the liquid palivizumab group, with an overall rate of 0.3% for both treatment groups combined. Given these observations and the number of subjects studied, the true immunogenicity rate (based on the upper limit of the exact 95% CI) is at most 2.9% for the lyophilized palivizumab group, 1.9%for the liquid palivizumab group, and 1.5% for both treatment groups combined.

- Safety results

A total of 30 (7.3%) out of 413 subjects reported SAEs during the conduct of the study.

There was a slight increase in subjects who experienced an SAE in the liquid palivizumab group compared to the lyophilized palivizumab group (5.9% lyophilized palivizumab; 8.5% liquid palivizumab) but these events were generally consistent with the underlying conditions in this pediatric age group. None of these SAEs were judged to be related to study drug. No subjects were discontinued from study drug dosing for any AE or SAE. One subject in the lyophilized palivizumab group died from reported asphyxia due to accidental suffocation after receiving four doses of study drug, and the death was considered by the investigator to be unrelated to the study drug.

CHMP's comment:

The immunogenicity of the liquid and lyophilized formulations of palivizumab 240-300 days post final dose was examined in this study. The frequency of detection of anti-palivizumab antibodies was low. The true immunogenicity rate for both treatment groups combined (as calculated by the upper limit of the 95% CI) was less than 1.5% and was not higher than 2.9% and 1.9% for lyophilized and liquid palivizumab groups, respectively.

Study MI-CP110. A Pivotal Phase 3 Study of MEDI-524 (Numax), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prophylaxis of Serious RSV Disease in High-Risk Children

Description

Methods

- Objectives

The primary objective of this study was to compare the safety and efficacy of motavizumab to palivizumab when administered monthly by intramuscular (IM) injection for the reduction of the incidence of RSV hospitalization among children at high risk for serious RSV disease.

The secondary objectives of this study were:

1. To compare the incidence of medically-attended lower respiratory tract infections (LRIs) between treatment groups

2. To compare the incidence of RSV-specific medically-attended LRI in a subset of patients

3. To compare the frequency and incidence of medically-attended otitis media (OM) infections between treatment groups

4. To compare the frequency of prescribed antibiotics for medically-attended LRI and medically-attended OM infections

5. To describe the trough serum concentrations of motavizumab

6. To describe the immunogenicity of motavizumab

- Study design

This was a Phase 3, randomized, double-blind, palivizumab-controlled, multi-center, multinational trial. Children were randomized in a 1:1 ratio to receive motavizumab or palivizumab at 15 mg/kg by IM injection every 30 days for a total of 5 injections. Randomization was blocked by study site and stratified according to the presence/absence of chronic lung disease (CLD) of prematurity requiring medical intervention/management. All patients were evaluated just prior to each injection of study drug with a final post dosing follow-up at Study Day 150. The trial was conducted during 2 consecutive northern hemisphere seasons with an intervening RSV season in the southern hemisphere. Each child only participated during a single RSV season.

- Study population /Sample size

The patients were: 1) children ≤24 months of age with a diagnosis of CLD of prematurity requiring medical intervention/management (i.e., supplemental oxygen, bronchodilators, or diuretics) within the 6 months before randomization, or 2) children born at ≤35 weeks gestational age (GA) at birth and ≤6 months of age at randomization.

Approximately 6600 patients were planned for enrollment.

- Treatments

Test product: Motavizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of motavizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidinehydrochloride.

Reference product: Palivizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of palivizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine.

- Outcomes/endpoints

Efficacy: Patients were evaluated just prior to each injection of study drug, with a final post dosing follow-up evaluation at Study Day 150. Patients were monitored throughout the trial for all hospitalizations, medically-attended LRIs, and medically-attended OM. Patients hospitalized for respiratory illness, or who developed a respiratory illness during hospitalization, were to be assessed for RSV by diagnostic testing of respiratory secretions. RSV testing was performed centrally using a validated, real-time RT-PCR RSV diagnostic test. For a subset of patients, RSV diagnostic testing of nasal secretions was performed in the event of medically-attended outpatient lower respiratory illness. All sites participating in this trial were solicited to be among the subset RSV-specific LRI population. Those centers which agreed to participate were required to involve the entire population randomized at the site.

Safety: Adverse events (AEs), serious adverse events (SAEs), and concomitant medications were collected from the period immediately following the first administration of study drug through Study Day 150. Blood was also collected prior to the first and last dose of study drug for safety evaluations.

Pharmacokinetics and Immunogenicity: Serum for measurement of anti-motavizumab antibodies and motavizumab concentrations was collected prior to the first and last dose of study drug. Additionally, all patients were randomly assigned to have blood collected prior to the second, third, or fourth injection of study drug for these evaluations.

- Statistical Methods

All tabular summaries were presented by treatment group. In general, categorical data were summarized by the number of patients falling within each category. Continuous variables were summarized by descriptive statistics including mean, standard error or deviation, median minimum, and maximum.

The primary efficacy endpoint was the incidence of RSV hospitalization from randomization through Study Day 150. The analysis was based on protocol-specified central RSV test results from the respiratory secretions analyzed via real-time RT-PCR. Respiratory hospitalizations with a positive result for this RSV test were counted in the primary analysis of RSV hospitalization. In addition, a new onset of lower respiratory symptoms in an already hospitalized child, with an objective measure of worsening respiratory status and a positive RSV test result, was counted as a primary endpoint. Deaths that could be demonstrated as caused by RSV (by autopsy or clinical history and virologic evidence) were also considered primary endpoints. The primary endpoint was evaluated by constructing a 2-sided 95% confidence interval (CI) around the observed relative risk (RR) of motavizumab compared to palivizumab. Motavizumab was to be declared non-inferior to palivizumab if the upper bound of the CI for RR was <1.265. If non-inferiority was declared then an assessment of superiority was to be made. Motavizumab was to be declared superior to palivizumab if the upper bound of the CI for RR was <1.

The secondary efficacy endpoints included the incidence of medically-attended LRI (including RSV-specific LRI), the frequency and incidence of medically-attended OM infections, and frequency of antibiotic use for LRI and OM. In general, a Cochran-Mantel-Haenszel approach stratified by presence or absence of CLD of prematurity requiring medical intervention/management was used. When the data were ordered, a row-mean score statistic was used. The categories that were used to evaluate the number of OM episodes were: no episodes, 1 episode, 2 episodes, and ≥3 episodes.

Comparisons between treatment groups were made for the total number of patients reporting at least one AE and at the system organ class level for all AEs, related AEs, SAEs, and fatalities using Fisher's exact test.

Results

- Recruitment/ Number analysed

A total of 6635 were randomized (3306 palivizumab; 3329 motavizumab) at 347 centers in 24 countries within the northern and southern hemispheres between 01/Nov/2004 and 09/Dec/2005.

- Baseline data

Each child participated in the study for a single RSV season, and approximately 98% completed the trial. A total of 97% of children in each treatment group received all 5 doses of study drug.

- Efficacy results

Motavizumab achieved its primary endpoint of non-inferiority compared to palivizumab in the reduction of RSV hospitalizations in this population of high-risk children. The overall RSV hospitalization rates in both groups were low, <2%. There were 26% fewer RSV hospitalizations in the motavizumab group compared to the palivizumab group [RR: 0.740, 95% CI: (0.503, 1.083)]. This finding was robust, with a non-inferiority p-value <0.01, based on the 99% CI. Motavizumab recipients had 50% fewer RSV-specific lower respiratory infections requiring outpatient medical treatment, in the pre-specified subset of sites participating in the nasal secretion sample collection for this endpoint, demonstrating statistical superiority of motavizumab over palivizumab (p=0.005). For each of the RSV-specific efficacy outcomes, consistency with the primary analysis was observed across subgroups.

- Safety results

Motavizumab and palivizumab demonstrated similar rates of AEs and SAEs, related AEs and SAEs, and study drug discontinuations. The majority (96%) of AEs were Level 1 or 2 in severity regardless of study drug treatment, and the incidence of Level 3 and 4 AEs was balanced between treatment groups. The most commonly reported AEs were upper respiratory tract infection (30.1% palivizumab vs. 29.1% motavizumab), pyrexia (16.9% vs. 16.4%), rhinitis (13.5% vs. 13.3%), and otitis media (12.8% vs. 13.1%)

AEs in the Skin and Subcutaneous Tissue Disorder system organ class were increased in the motavizumab group compared to the palivizumab group (20.7% and 18.5%, respectively).

Possible contributors to this difference were identified as AEs of rash (3.1%, palivizumab; 4.0%, motavizumab) and urticaria (0.3% palivizumab; 0.7%, motavizumab). Most of these events were mild, transient, and did not result in discontinuation of study drug. Skin events with preferred terms consistent with hypersensitivity that occurred within 2 days of a dose (8, 0.2% palivizumab vs. 22, 0.7% motavizumab), Level 3 or SAE events (0.0% vs. 9, 0.3%), and those that resulted in discontinuation of study drug (0.0% vs. 9, 0.3%) were infrequent but had a higher incidence in motavizumab recipients compared to children receiving palivizumab. Eight (0.2%) patients in the motavizumab group with specific skin events consistent with hypersensitivity were redosed without recurrences. There was no evidence of a difference between the two treatment groups with regard to respiratory events of interest that may be associated with hypersensitivity.

The overall mortality rates (4, 0.1% palivizumab; 8, 0.2% motavizumab) were not statistically significantly different between the treatment groups and lower than in a previous placebo-controlled study of palivizumab (MI-CP018). No death was considered to be related to study drug by the site investigators, and none were RSV-related. The rate of SIDS/sudden unexplained death in each treatment group was similar to or lower than the expected rate for high-risk infants.

- Immunogenicity:

A total of 22 (0.7%) children had anti-motavizumab binding activity (defined as a titer with a dilution of ≥1:10) at any time after the start of dosing, with titers ranging from 1:10 to 1:31250. An additional 7 patients had anti-motavizumab antibody detected pre-dose 1 but antibody was not detected at any time point post baseline in these patients. The incidence of immunogenicity in the motavizumab group was low, less than 1%, and comparable to the historical palivizumab rate (0.7% in the palivizumab group in MI-CP018 30 days following the fourth injection). There were no clinical safety effects that could be associated with detectable antibody.

- Pharmacokinetics:

Mean trough serum concentrations of motavizumab at 30 days post dose 1 were 45.95 µg/mL. Mean trough serum concentrations were 64.59, 80.24, and 88.52 µg/mL at 30 days post dose 2, 3, and 4, respectively. A small number of motavizumab patients (n=22, 0.7%) had detectable immunogenicity

at any time post baseline during the study. Mean trough serum concentrations of motavizumab for these children appeared lower after 2 doses of study drug, compared to children without detectable antibody. However, there were only a small number of observations at any one time point and there was marked variability in drug concentrations such that individual values for patients with detectable antibodies were within the range of those seen for patients without detectable antibody.

CHMP's comments:

In this phase III study including more than 6600 high risk children with prematurity and CLD of prematurity motavizumab demonstrated improved activity compared to palivizumab in the reduction of serious RSV disease. Furthermore, palivizumab and motavizumab were well-tolerated with comparable overall rates of AEs, SAEs, and AEs leading to discontinuation. Immunogenicity to palivizumab and motavizumab was low. As indicated previously, the development of motavizumab has been discontinued.

MI-CP124. A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), in Children with Hemodynamically Significant Congenital Heart Disease

Description

Methods

- Objectives

The primary objective was to describe the safety and tolerability of motavizumab when given monthly as prophylaxis against serious RSV infection among children with hemodynamically significant congenital heart disease (CHD).

The secondary objectives of this study were:

1. To describe the incidence of RSV hospitalization in children with hemodynamically significant CHD given motavizumab or palivizumab for prophylaxis against serious RSV disease
2. To describe the incidence of RSV outpatient medically-attended lower respiratory infection (MA-LRI) in each treatment group (for subjects randomized in Season 2 only)
3. To describe the pharmacokinetics and immunogenicity of motavizumab
4. To describe the effect of cardiopulmonary bypass on serum motavizumab concentrations

- Study design

A Phase 2, randomized, double-blind, palivizumab-controlled, multicenter, multinational study conducted over two RSV seasons (2005-2006 and 2007-2008) in the northern hemisphere. Each subject participated only during a single RSV season. Subjects were randomized in a 1:1 ratio to receive either 15 mg/kg motavizumab or 15 mg/kg palivizumab. Randomization was blocked by site and stratified by presence or absence of cyanotic CHD. Study drug was administered by intramuscular (IM) injection every 30 days during the RSV season for a total of 5 scheduled doses. Additionally, children who underwent cardiac surgery with cardiopulmonary bypass through Study Day 150 were to receive a protocol-specified replacement dose of study drug immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug were continued to be given according to the protocol-specified dosing schedule. All subjects were evaluated just prior to each injection of study drug with a final post dosing follow-up at Study Day 150.

- Study population /Sample size

The subjects in this study had to be ≤ 24 months of age at randomization with documented hemodynamically significant CHD that was unoperated or partially corrected. Approximately 1400 subjects were planned for enrollment.

- Treatments

Test product: Motavizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of motavizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidinehydrochloride.

Reference product: Palivizumab 15 mg/kg IM - provided in sterile vials containing 100 mg of palivizumab in 1 mL of a sterile preservative-free liquid product at pH 6.0, formulated with 25 mM histidine, and 1.6 mM glycine.

The products were administered every 30 days for a total of 5 doses.

- Outcomes/endpoints

Safety: Adverse events (AEs), serious adverse events (SAEs), and concomitant medications were collected from the period immediately following the first administration of study drug through Study Day 150. Blood was collected prior to the first and last doses of study drug for serum chemistries (AST, ALT, BUN, and creatinine) as part of the safety evaluation; vital signs were measured prior to and 30 minutes after each dose of study drug. Subjects were evaluated just prior to each dose of study drug, with a final post-dosing follow-up evaluation at Study Day 150.

Efficacy: Subjects were monitored throughout the study for all hospitalizations during Seasons 1 and 2 and for outpatient medically-attended lower respiratory (MA-LR) illnesses during Season 2. Subjects hospitalized for a cardiac/respiratory illness (other than planned surgical procedures not associated with an acute illness), or whenever a cardiac/respiratory deterioration occurred during an admission, were assessed for RSV by diagnostic testing of respiratory secretions. Subjects with an outpatient MA-LR illness had nasal secretions collected that were tested for RSV. RSV testing was performed centrally using a validated real-time reverse-transcriptase polymerase chain reaction (RT-PCR) RSV diagnostic test for RSV A and RSV B.

Pharmacokinetics (PK) and Anti-Drug Antibodies (ADA): Serum was collected from all subjects pre-Dose 1 and 30 days post-Doses 1 and 4 (Study Days 0, 30, and 120) for measuring trough serum concentrations of motavizumab and ADA to palivizumab and motavizumab. Additionally, all subjects were randomly assigned to have an additional blood sample collected 30 days post-Doses 2 or 3 (Study Days 60 or 90) for these evaluations. Trough serum concentrations of motavizumab were determined centrally by a validated enzyme-linked immunosorbent assay (ELISA). Anti-drug antibody to motavizumab was determined centrally by an ELISA-based method, which was the original validated assay used for the detection of ADA. During the course of the study, a drug-tolerant electrochemiluminescent assay (ECLA) was developed. Samples were tested for ADA to motavizumab by both assay methods. Anti-motavizumab antibodies were tested for samples obtained at any time during the study using the ELISA-based method and for each motavizumab subject's last available post-baseline sample using the ECLA-based method. A motavizumab subject was counted as having ADA if detected by ECLA or by ELISA if ECLA testing was not performed due to lack of sample. ADA to palivizumab was tested for each subject's last available post-baseline sample using the ECLA-based method only. Subjects who had ADA to palivizumab or motavizumab detected by ECLA or by ELISA if ECLA testing was not performed were tested for drug-specific IgE ADA using ECLA.

- Statistical Methods

Safety and tolerability were assessed primarily by summarizing AEs and SAEs that occurred through Study Day 150 (ie, 30 days post-Dose 5); AEs and SAEs that began after Study Day 150 were not collected or summarized. Adverse events and SAEs were summarized by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA; Version 11.1), and by severity and relationship to study drug. Subjects were counted only once for each preferred term, once for each SOC, and by the highest event severity, regardless of how many events the subject experienced. Additionally, AEs and SAEs were summarized by CHD stratum and primary cardiac lesion. Comparisons between treatment groups were made for the total number of subjects reporting at least 1 AE and at the SOC level using a two-sided 95% exact confidence interval (CI) and the p-value for the rate difference. Statistical comparisons between treatment groups did not account for multiple comparisons and no statistical comparisons were performed within each stratification factor.

The incidence of RSV hospitalization from Study Day 0 through Study Day 150 was summarized for each treatment group. Subjects with multiple RSV hospitalizations were counted once even if hospitalized more than once for RSV. RSV hospitalization endpoints included both primary (cardiac/respiratory hospitalizations with a positive real-time RT-PCR

RSV diagnostic test) and nosocomial RSV hospitalizations (new onset of lower respiratory tract symptoms with an objective measure of study-defined worsening respiratory status in an already hospitalized subject with a positive real-time RT-PCR RSV diagnostic test), as well as deaths that could be demonstrated as caused by RSV (based on virologic evidence and either clinical history or autopsy). Only subjects randomized in Season 2 were monitored for the incidence of RSV outpatient MA-LRI from Study Days 0 through 150 and this was summarized for each treatment group. Subjects were counted once, regardless of how many RSV outpatient MA-LRI events occurred. Rates of primary RSV hospitalization and RSV outpatient MA-LRIs were evaluated to compare motavizumab to palivizumab by constructing a two-sided 95% CI around the observed relative risk. Additionally, the analysis included a two-level categorical covariate to control for CHD stratum.

Other secondary objectives of this study included describing the PK of motaivuzmab, ADA to palivizumab and motavizumab, and the effect of cardiac surgery with cardiopulmonary bypass surgery on serum motavizumab concentrations. Mean trough serum concentrations of motavizumab were summarized overall, by CHD stratum, and by subjects with and without detectable ADA for the motavizumab group using means, standard deviations, medians, and ranges at each study collection time point. Serum samples collected after subjects underwent cardiac surgery with cardiopulmonary bypass but before receiving a replacement dose were not included in the analysis of trough motavizumab concentrations. The number and percentages of subjects with ADA to motavizumab detected (titer ≥ lower limit of quantitation), not detected, or not tested were summarized for both the ELISA- and ECLA based methods, while the number and percentages of subjects with ADA to palivizumab were summarized for the ECLA-based method only. Additionally, summaries were provided for drug-specific IgE ADA, which was tested in palivizumab and motavizumab subjects who exhibited ADA.

Results

- Recruitment/ Number analysed

A total of 1236 subjects (612 palivizumab, 624 motavizumab) were randomized at 162 sites (61 North America, 73 European Union, and 28 ROW) in 16 countries within the northern hemisphere between 21Oct2005 and 14Dec2005 in Season 1 and 02Oct2007 and 31Dec2007 in Season 2. One subject was withdrawn from the study as per the local Ethics Committee, which deemed that this subject's data could not be used for analysis purposes; data for this subject were not included in this study report.

- Baseline data

Each subject participated in the study for a single RSV season, and approximately 97% of subjects in each treatment group completed the study. Approximately 95% of subjects in each treatment group received all 5 scheduled doses of study drug.

- Efficacy results

Data were collected for the efficacy endpoints of RSV hospitalization (Seasons 1 and 2) and RSV outpatient MA-LRI (Season 2); however, the study was not powered to detect statistically significant between-group differences in the efficacy endpoints. The overall rates of RSV hospitalization were low in both treatment groups and noted to be lower in motavizumab recipients than in palivizumab recipients (16 [2.6%] palivizumab, 12 [1.9%] motavizumab). A 25% (RR: 0.746; 95% CI: 0.344, 1.586) relative reduction in RSV hospitalization was observed in children who received prophylaxis with motavizumab versus palivizumab. During Season 2 when subjects were monitored for medically-attended outpatient lower respiratory illnesses, again, the overall rates were low in both treatment groups and the incidence of RSV outpatient MA-LRI was noted to be lower in motavizumab recipients than in palivizumab recipients (6 [1.9%] palivizumab, 3 [1.0%] motavizumab). A 50% (RR: 0.495; 95% CI: 0.101, 1.989) relative reduction in RSV-specific lower respiratory tract infections requiring outpatient medical attention was observed in motavizumab recipients compared with palivizumab recipients.

Pharmacokinetics: Trough serum concentrations of motavizumab, excluding serum concentrations after cardiac surgery with cardiopulmonary bypass, increased with each successive monthly dose of study drug from a mean ± SD of 46.90 ± 15.20 µg/mL at 30 days post-Dose 1 to 60.94 ± 25.41, 66.59 ± 34.51, and 77.87 ± 32.75 µg/mL at 30 days post-Doses 2, 3, and 4, respectively.

These trough levels were similar to those that included serum concentrations after cardiac surgery with cardiopulmonary bypass and a replacement dose (46.62 ± 15.46, 60.19 ± 25.50, 65.71 ± 34.17 and 79.09 ± 34.05, µg/mL, at 30 days post-Doses 1, 2, 3, and 4, respectively), indicating that the replacement dose after cardiac surgery with cardiopulmonary bypass was adequate for maintaining motavizumab concentrations in the same range as for children who did not undergo cardiac surgery with cardiopulmonary bypass. Trough serum concentrations were below detectable levels in 1 to 3 children at various time points during the study. When analyzed by CHD stratum, mean trough serum concentrations of motavizumab were similar between the 2 strata. A small number of motavizumab subjects (9 [1.5%]) had detectable ADA at any time post baseline during the study. Mean trough serum concentrations of motavizumab for these children were lower at most time points evaluated compared to children without detectable ADA.

- Safety results

Motavizumab and palivizumab subjects demonstrated similar rates of AEs and SAEs, related AEs and SAEs, and study drug discontinuations; 1 palivizumab subject and no motavizumab subjects had study drug discontinued by the site investigator due to an AE. Approximately 93% of subjects in both treatment groups had an AE reported, which is as expected for this High-risk study population of children with CHD. The majority of subjects had AEs of Level 1 or Level 2 as the highest severity level, regardless of study drug treatment, and the incidence of Level 3 and Level 4 AEs was balanced between treatment groups. The most commonly reported AEs were those expected to occur in this pediatric population and included pyrexia (29.2% palivizumab vs 29.8% motavizumab), upper respiratory tract infection (28.1% vs. 27.3%), cough (11.6% vs. 14.9%), rhinitis (12.6% vs 14.7%), and otitis media (11.4% vs. 12.5%). Furthermore, mortality rates were comparable between the treatment groups (10 [1.6%] palivizumab, 9 [1.5%] motavizumab). No deaths were deemed related to study drug and none were reported as RSV-related, attributable to SIDS or reported as a sudden

unexplained death by the site investigator. However, 4 deaths in each treatment group were assigned the designation of a sudden unexplained death by the MAH Medical Monitor because these deaths occurred outside the hospital or emergency department with no definitive cause or autopsy performed.

Additionally, AEs of interest categories were analyzed and included Possible Hypersensitivity Events (MAH-defined Skin and Respiratory Events of Interest and Standardized MedDRA Queries [SMQ]-defined Angioedema and Anaphylactic Reactions), Injection Site Reactions, Elevated Hepatic Transaminases, Apnea/Breathing Abnormalities, and Neurologic Events.

The incidence of skin events in the Skin and Subcutaneous Tissue Disorder SOC and by MAH-defined skin events of interest classification was approximately 3% higher in the motavizumab group than the palivizumab group. All events consistent with immediate hypersensitivity reactions, which would typically occur within 2 days of a study drug dose, were identified by the analyses for MAH-defined Skin and Respiratory Events of Interest. No new events within 2 days of study drug dosing were captured by the Angioedema or Anaphylaxis SMQs. Respiratory events were reviewed and were not consistent with hypersensitivity reactions. Skin events within 2 days of a study drug dose occurred in 7 (1.1%) palivizumab and 14 (2.3%) motavizumab subjects. Most (80%) of these events were Level 1 or Level 2 in severity; Level 3 events or SAEs occurred in 2 (0.3%) palivizumab and 8 (1.3%) motavizumab subjects, while no events were Level 4 in severity. Of these 21 subjects with skin events within 2 days of a study drug dose, 8 (3 palivizumab, 5 motavizumab) experienced the event after the last study drug dose with no subsequent doses given, while 13 subjects (4 palivizumab, 9 motavizumab) were redosed with 1 motavizumab subject experiencing a recurrence of the event; this event of erythema recurred within 2 days of the last study drug dose, was Level 1 in severity, and resolved within 1 day of onset without treatment. No events consistent with anaphylaxis were identified in either treatment group. Additionally, multiple analyses were conducted to identify possible hypersensitivity events with a late onset (>2 days after dosing) that would be consistent with a severe cutaneous reaction. In the majority of subjects with skin events of interest, the event occurred beyond 2 days of dosing (36/44 [81.8%] palivizumab, 45/63 [71.4%] motavizumab); most of these events were Level 1 or Level 2 in severity, transient, and did not recur with subsequent doses. Two subjects in the motavizumab group had events reported as erythema multiforme. From the details available for these events, it appeared that both cases would be considered erythema multiforme minor; 1 subject was redosed without recurrence, while the other subject was not redosed. There was no evidence in either treatment group of events that would be consistent with more severe reactions such as erythema multiforme major, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

In each of the remaining AEs of interest categories (Injection Site Reactions, Elevated Liver Transaminases, Apnea/Breathing Abnormalities, and Neurologic Events), the overall incidence of events was numerically lower in the motavizumab group compared with the palivizumab group (percentage-point differences ranging from 0.3% to 2.5%). In regards to cardiac procedures, there were numerically more planned and urgent procedures performed in more palivizumab than motavizumab subjects.

Anti-Drug Antibodies: In this study, there was a similar rate of detectable ADA to palivizumab and motavizumab for subjects receiving the corresponding monoclonal antibody (9 [1.5%] palivizumab by ECLA, 9 [1.5%] motavizumab by ELISA/ECLA). No IgE was detected in any subject who exhibited ADA in either treatment group. All palivizumab and motavizumab subjects who exhibited ADA had ≥ 1 AE reported. Within each treatment group, the type and frequency of AEs in subjects with detectable ADA were similar to those in subjects without detectable ADA, and between treatment groups, the type and frequency of AEs in subjects who exhibited ADA were generally balanced as well. In the motavizumab group, 3 subjects with detectable ADA had a skin event of interest; all 3 events were transient and none recurred with subsequent study drug doses, thus, making an association between the event and

ADA unlikely. No palivizumab subjects with detectable ADA had a skin event of interest. Of the subjects who exhibited ADA in either treatment group, 1 subject in the palivizumab group was hospitalized for RSV, and none of the subjects in either treatment group had a RSV outpatient MA-LRI.

CHMP's comments:

In this Phase II study motavizumab was compared to palivizumab with regard to safety, immunogenicity and efficacy in a randomized, double-blind design. 1236 children less than 2 years of age with hemodynamically significant congenital heart disease were enrolled. The 2 groups had similar overall rates of AEs and SAEs, but motavizumab recipients had approximately a 3% higher incidence of in Skin and Subcutaneous tissue disorders SOC events and sponsor-defined skin events of interest. Approximately 93% of subjects in both treatment groups had an AE reported, which was as expected for this high-risk study population of children with CHD. The most commonly reported AEs were pyrexia (29.2% palivizumab versus 29.8% motavizumab), upper respiratory tract infection (28.1% versus 27.3%), cough (11.6% versus 14.9%), rhinitis (12.6% versus 14.7%), and otitis media (11.4% versus 12.5%).

Mortality rates were comparable between the treatment groups (10 [1.6%] palivizumab, 9 [1.5%] motavizumab). No deaths were judged related to study drug and none were reported as RSV-related.

The incidence of ADA to palivizumab and motavizumab was low (1.5% in both groups). No IgE was detected in any subject who exhibited ADA.

The study was not powered to detect statistically significant between-group differences in efficacy endpoints; however, relative reductions of 25% in RSV hospitalization (16 [2.6%] palivizumab, 12 [1.9%] motavizumab).and 50% in RSV outpatient MA-LRI were observed in subjects who received monthly doses of motavizumab compared with palivizumab. As indicated previously, the development of motavizumab has been discontinued.

Discussion on clinical aspects

CHMP's overall conclusion and recommendation

The MAH for Synagis, palvizumab, has submitted 7 clinical studies in accordance with Article 46 of Regulation (EC) No1901/2006.

Two of the studies are small uncontrolled studies of the safety and efficacy of palivizumab in special populations: 28 Japanese children with immunocompromised medical conditions in study M12-420 and 94 Russian infants at high risk of severe RSV infection in Study W10-664.

Two of the studies are randomized, double-blind studies comparing palivizumab to motavizumab. In the phase II Study MI-CP124 including 1236 children below 2 years of age with hemodynamically significant CHD the primary endpoint was safety and tolerability; in the phase III Study MI-CP110 including 6635 children ≤ 24 months of age with CLD of prematurity or ≤ 35 weeks gestational age at birth the primary objectives were safety and efficacy.

In one phase II, randomized, double-blind study including 260 children at high risk for RSV infection (Study MI-CP127) the primary objective was to evaluate safety, tolerability and immunogenicity of palivizumab and motavizumab when administered to the same subjects within the same season.

Study MI-CP118, a phase 1/2 randomised, double-blind study, evaluated the immunogenicity, pharmacokinetics and safety of palivizumab and motavizumab when administered to 136 children who in the previous RSV-season had motavizumab in another clinical trial.

As indicated previously, the development of motavizumab has been discontinued.

Finally, in the phase IV study MI-CP116 the lyophilized and the liquid formulations of palivizumab were compared with regard to immune reactivity in 417 children at high risk for RSV infection.

The MAH has for each study submitted a Clinical Overview; however a Clinical Overview summarizing the 7 studies has not been provided. From the Cover Letter it appears that the MAH is of the opinion that Studies M12-420, W10-664, MI-CP118 and MI-CP127 do not influence the benefit-risk balance for palivizumab and therefore do not require regulatory action on the marketing authorization. The CHMP agrees in this conclusion. No data from children with immunocompromised medical conditions are included in the currently approved SmPC for palivizumab; however the results of Study M12-420 are not strong enough (open-label study in 28 children) to qualify for implementation in the SmPC.

The results of Study MI-CP127, demonstrated that palivizumab and motavizumab can be used interchangeable; however, as indicated previously, the development of motavizumab was discontinued. Hence, this information is irrelevant for the palivizumab SmPC.

The MAH claims that studies MI-CP116, MI-CP110 and MI-CP124 will be submitted as supportive clinical experience in an extension application consisting of the full relevant data package to register the solution for injection formulation in the EU in October 2013. Hence, the impact of these studies on the SmPC will be assessed with this procedure. Of note, the data on anti-human antibody to palivizumab from these 3 studies have been included in the EU SmPC section 4.8 as a result of variation II/77.

Overall conclusion

Results from the 7 studies submitted in accordance with Article 46 of the Paediatric Regulation are in agreement with the currently approved SmPC and no further regulatory action is deemed necessary.

Recommendation

No regulatory action required

Additional clarifications requested

Not applicable