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Procedure Management and Committees Support Division

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

Synagis

palivizumab

Procedure no: EMEA/H/C/000257/P46/044

Note

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

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1. Introduction

On November 19, the MAH submitted a final study report for the post-marketing observational paediatric study p14-579, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been provided.

The MAH states, that the safety and effectiveness of this study is consistent with the previously established benefit risk profile of Synagis and does not recommend any changes to the SmPC.

Scientific discussion

1.1. Information on the development program

The MAH stated that:

Study P14-579: "Prospective, Multi-Center, Observational Program to Assess RSV Hospitalization Rate in a Population of Children at High-risk of Serious RSV Illness who received Palivizumab Immunoprophylaxis in Routine Clinical Setting in the Russian Federation

The MAH confirms that this study is a stand-alone study and does not form part of a development programme.

1.2. Information on the pharmaceutical formulation used in the study.

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 were subsequently conducted in different patient groups. The currently approved indications 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 study 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. All participants received IM injections according to the local label, which recommends a 1 month injection window between consequential 5 palivizumab injections at a dose of 15 mg/kg.

1.3. Clinical aspects

1.3.1. Introduction

Synagis (Pavalizumab) received marketing authorization through the centralised procedure in 2009. Synagis was approved 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 six months of age at the onset of the RSV season;

-children less than two years of age and requiring treatment for bronchopulmonary dysplasia (BPD) within the last six months;

- Children less than two years of age and with haemodynamically significant congenital heart disease (CHD).

The MAH submitted a final report for:

> P14-579: Prospective, Multi-Center, Observational Program to Assess RSV Hospitalization Rate in a Population of Children at High-risk of Serious RSV Illness Prescribed for Palivizumab Immunoprophylaxis in Routine Clinical Setting in the Russian Federation.

Description

Methods

Objective

The primary objective of the study was to assess LRTI hospitalization rate with positive RSV laboratory diagnostic test of respiratory secretions and death due to RSV infection in population of infants at high-risk of serious RSV illness (infants born ≤ 35 weeks of gestation and infants ≤ 24 months with BPD or CHD) who received immunoprophylaxis during the RSV season.

In addition the study assessed several secondary objectives, which primarily evaluated the severity of disease.

Study design

This was a Phase 4, prospective, multicenter, non-interventional, non-comparative, study that took place in 16 clinical sites located in different regions of Russia. Participants were recruited and observed in national and regional neonatal centres/hospitals. Immunoprophylaxis with palivizumab was given during the RSV season from October 2014 through April 2015 in routine clinical settings in the Russian Federation.

Inclusion Criteria

1. Planned prescription of palivizumab for immunoprophylaxis during RSV season or patients to whom palivizumab was prescribed and who received the first dose of palivizumab no later than 60 day before enrolment in the study.
2. Infants at high risk of severe RSV infection defined as fulfilling at least one of the following:
    - Infants born ≤ 35 weeks gestational age AND are ≤ 6 months of age at the onset of the RSV season;
    - Infants ≤ 24 months of age AND with a diagnosis of BPD (defined as oxygenrequirement at a corrected gestational age of 36 weeks);

- Infants ≤ 2 4 months of age with hemodynamically significant CHD, unoperated or partially corrected.

Exclusion Criteria
1. Major congenital malformation aside from CHD.
2. Chronic pulmonary disease other than BPD.
3. Acute period of any infection.
4. Contraindication to palivizumab prescription according to local label.
5. Administration of a product possibly containing RSV-neutralizing antibody within 30 days prior to enrollment or current administration (includes, but is not restricted to, the following: RSV hyperimmunoglobulin, polyclonal intravenous immunoglobulin, cytomegalovirus hyperimmunoglobulin, varicella zoster hyperimmunoglobulin).
6. Previous enrollment in this program.

Study population:

Starting on 22 October 2014 and ending on 20 February 2015, a total of 359 patients were enrolled in the study at 16 clinical sites in the Russian Federation.

Treatments

All participants received intramuscular injections of palivizumab according to a physicians' prescription and the local Russian label. The labeling recommends 1 month injection window between sequential 5 palivizumab IM injections. It is recommended to administer the first injection right before the anticipated start of the RSV season. Participants could receive from 3 to 5 monthly injections of palivizumab during the 2014 – 2015 RSV season and duration of this program.

Outcomes/endpoints:

Primary endpoint: The proportion of infants among the study population who were hospitalized for LRTI with a positive laboratory diagnostic test for RSV from respiratory secretions or who died due to RSV infection confirmed by autopsy or clinical history and virologic evidence.

Safety: Spontaneously reported non-serious Adverse Events (AEs) and serious AE through the study period.

Statistical Methods:

As this was a descriptive study, summary statistics are provided. The Safety Analysis Set (SAS) included all patients who signed patient authorization form to participate in the study and had any collected data.

Results

Recruitment/ Number analysed

Starting on 22 October 2014 and ending on 20 February 2015, a total of 359 patients were enrolled in the study at 16 clinical sites in the Russian Federation. Overall, 86.9% (n = 312) of children received three or more planned injections of palivizumab 22.6% (n = 81) of children missed or had a delayed palivizumab injection of at least 10 days. Forty-two percent (n = 153) of patients completed the study. A high rate of non-compliance with the optimal schedule was seen: 22.6% of infants received at least one palivizumab injection after incorrect dose timing (missed or delayed for more than 10 days

injection). More than half of patients (57.4%) discontinued the immunoprophylaxis with palivizumab prematurely, the main reason of early discontinuation was related to the lack of study drug.

Baseline data

Median age of infants enrolled in the study was 2.0 months (range from 0 to 21.0 months). The numbers of males were 180 and females 179 patients. The patient population belonged predominantly to the white race (93.6%).
Bronchopulmonary dysplasia was diagnosed in 148 (41.2%) infants; the median duration of diagnosis was 3.45 months with a range of 0 to 19.1 months. Congenital heart disease was found in 45 (12.5%) patients, median duration of diagnosis was 4.01 months with a range of 0.3 to 17.3 months.

The mean gestational age of infants was 29.4 (± 3.0) weeks, the mean birth weight – 1.298 (± 0.473) kg. The majority of infants (289 patients or 80.5%) required resuscitation, 335 (93.3%) of patients were admitted to neonatal or pediatric intensive-care unit (NICU/PICU). The median duration of hospitalization to NICU/PICU was 26 days (range 1 to 137 days). Almost all patients (344 patients or 95.8%) required assisted ventilation: continuous positive airway pressure (CPAP) was required in 122 (34.0%) infants, mechanical ventilation – in 84 (23.4%) infants, combined method (CPAP and mechanical ventilation) was used most often – in 138 (38.4%) patients. Surfactant was used in the majority of patients (265 patients or 73.8%).

Efficacy results

Overall, 86.9% (n = 312) of children received three or more planned injections of palivizumab. 22.6% (n = 81) of children missed or had a delayed palivizumab injection of at least 10 days. Forty-two percent (n = 153) of patients completed the study.
In total, 12 hospitalizations due to LRTI were reported during the study among 11 patients (3.1%; 95% CI 1.5, 5.4).
A RSV diagnostic test was performed in 9 of the 11 cases of LRTI hospitalization.
Subsequently, one case of RSV positive LRTI was detected, resulting in a RSV LRTI hospitalization rate of 0.3% (1/359). The infant hospitalized for RSV positive LRTI was born prematurely (27 weeks gestational age) and was diagnosed with bronchopulmonary dysplasia.
The patient received 3 injections of palivizumab, the last injection was received 15 days before hospitalization. The duration of the RSV-positive hospitalization was 46 days, including 35 days in the ICU. The RSV-positive pneumonia resolved in this patient.

Safety results

Forty-one treatment emergent adverse events (AEs) were reported in 19 of 359 (5.3%) subjects through 30 days following the last observation visit. No AE led to discontinuation of palivizumab. No AEs exceeded a 5 % frequency threshold. The most common AE was viral respiratory tract infection with a rate of 1.9% (n = 7) followed by bronchitis (1.4%, n = 5) and pneumonia (1.4%, n = 5).

Nine AEs in 3 subjects (0.8%) were assessed as possibly related to palivizumab and included bronchopneumonia, pneumonia, viral respiratory tract infection, apnoea, BPD, dyspnea, cough, decreased appetite and lethargy.

Thirty-three serious adverse events (SAEs) were reported among 17 (4.7%) subjects through 30 days following the last observation visit. The most frequent SAE were pneumonia (7 or 2.0% of patients), viral respiratory tract infection (6 or 1.7% of patients) and bronchitis (5 or 1.4% of patients). 4 (1.1%) patients with combined pathology died during the study, two of them had pneumonia. No cases of death due to RSV infection were reported in this study.

1.3.2. Discussion on clinical aspects

In this postmarketing observational study, the hospitalization rate for LRTI was low with 12 LRTI reported among 11 of 359 infants (3.1%, 95% CI 1.5-5.4%). These data is based on a small Russian population, since more than half of the enrolled subjects did not complete the study and since many children either missed or had delayed injections due to shortage of palivizumab. Only a single case of confirmed RSV LRTI hospitalization among the 359 patients was observed (0.3%). As regards safety, the overall safety data was consistent with the safety profile previously established for palivizumab; few drug related AE were observed and no AE led to the discontinuation of palivizumab.

2. Rapporteur's overall conclusion and recommendation

Synagis is already approved.

The P14-579 Russian observational study in Russia was a supportive study, which aimed to assess the RSV-associated LRTI rate, deaths and safety in a "real world" target population for palivizumab.

The study has several important limitations:

A high percentage of the enrolled infants- 58% (n=206) did not complete the study. Notably, 23% (n=81) of the children missed or had delayed palivizumab injections of at least 10 days. The main cause for the early discontinuations was lack of palivizumab, which occurred in 185 (90%) of these cases. However, no patients discontinued study participation due to adverse events.

A single hospitalization of patient with confirmed positive RSV was reported. However, in only 8 of the 12 hospitalizations due to LRTI a RSV diagnostic test was done. Among these, 8 patients were tested by a rapid antigen test system and in one patient the laboratory test system was not specified. Palivizumab may directly interfere with immune-based RSV diagnostic tests, such as the antigen detection-based assay used in the study. An important limitation for the study is therefore that the RSV-related hospitalization in reality may have been higher, since 4 of the 12 hospitalized infants were not RSV-tested and the diagnostic tests may have been false-negative.

With these important limitations, it is hard to interpret the study. However, even with these limitations, the findings from this observational study seem overall consistent with the established efficacy and safety of palivizumab. The results from study p14-579 submitted in accordance with article 46 of the Pediatric Regulation are in agreement with the currently approved SMPC and no further regulatory action is deemed necessary.

☒ Fulfilled:

No regulatory action required.