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Human Medicines Evaluation 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/P46/050

Note

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

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1. Introduction

On December 2017, the MAH submitted a final study report for the post-marketing observational paediatric study M15-539, 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 and confirms that:

Study M15-539: "A Prospective, International, Multicenter, Open-Label, Non-Controlled Study of Safety and Effectiveness of Palivizumab, in Children at High Risk of Severe Respiratory Syncytial Virus (RSV) Infection in the Russian Federation and the Republic of Belarus",- 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 originally approved lyophilized formulation, is currently the only formulation approved in the Russian Federation.

In the EU, the liquid solution for injection formulation of palivizumab has also been approved since August 2014.

1.2.1. Introduction

Synagis (Pavalizumab) received marketing authorization through the centralised procedure in 1999. 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 (HSCHD).

The MAH submitted a final report for:

Study M15-539 titled "A Prospective, International, Multicenter, Open-label,Non-Controlled Study of Safety and Effectiveness of Palivizumab, in Children at High Risk of Severe Respiratory Syncytial Virus Infection in the Russian Federation and the Republic of Belarus."

Methods

Objective

The primary objective of this study was to collect further data on safety and effectiveness of the liquid formulation of palivizumab administered as monthly intramuscular (IM) injections among preterm infants, infants with BPD, and infants with hemodynamically significant congenital heart disease in the Russian Federation and the Republic of Belarus.

In addition, the study aimed to assess several secondary objectives, which primarily evaluated the severity of disease.

Study design

This was a phase 3b, prospective, multicenter, open-label, non-controlled study of immunoprophylaxis with the intramuscular (IM) administration of palivizumab for the prevention of severe lower respiratory tract RSV infection in infants at high-risk of severe RSV infection (preterm infants, infants with BPD , and infants with HSCHD. The study was conducted over one RSV season (2016 – 2017) in the Russian Federation and the Republic of Belarus in routine clinical settings.

Inclusion Criteria
Infants at high risk of severe RSV infection defined as preterm infants born ≤ 35 weeks GA and ≤ 6 months of age at enrollment; and/or infants ≤ 24 months of age at enrollment with a diagnosis of BPD requiring intervention/management any time within 6 months prior to enrollment; and/or infants ≤24 months at enrollment with HSCHD (either cyanotic or acyanotic; unoperated or partially corrected).

Exclusion Criteria
1. Hemodynamically insignificant small atrial or ventricular septal defects, patent ductus arteriosus, aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone.
2. Hospitalized at the time of enrollment
3. On mechanical ventilation at the time of enrollment (including continuous positive airway pressure [CPAP]).
4. Life expectancy of < 6 months
5. Unstable cardiac or respiratory status (including severe cardiac defects)
6. Active respiratory illness or other acute infections.
7. Renal or hepatic impairment
8. Unstable neurological disorder
9. Immunodeficiency (including Human immunodeficiency Virus [HIV])
10. Allergy to Ig products.

Study population:
Infants at high risk of severe RSV infection defined as preterm infants born ≤ 35 weeks GA and ≤ 6 months of age at enrollment; and/or infants 24 months of age at enrollment with a diagnosis of BPD requiring intervention/management any time within 6 months prior to enrollment; and/or infants ≤24 months at enrollment with HSCHD (either cyanotic or acyanotic; unoperated or partially corrected)

Treatments

Palivizumab was administered prophylactically every 30 days during the 2016/2017 RSV season. 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.

Outcomes/endpoints:

Primary endpoint: Rate of hospitalization due to RSV infection.

Secondary endpoints, for subjects with RSV hospitalization, were:
-Total number of hospitalization days.
-Use of increased supplemental oxygen or increased mechanical ventilation
-Total number of hospitalization days with use of increased supplemental oxygen or increased mechanical ventilation
-Number and duration of ICU hospital stays.

Statistical Methods:

Since the study was non-controlled only descriptive statistics are provided.

Results

Recruitment/ Number analysed

A total of 50 subjects were enrolled and treated at 7 study sites located in the Russian Federation (6 sites) and the Republic of Belarus (1 site), and all 50 subjects were included in the effectiveness (ITT set) and safety (Safety set) analysis . Of these 50 subjects, 34% were premature infants born ≤ 35 weeks GA and ≤ 6 months of age at enrollment, 30% were infant's ≤ 24 months of age at enrollment with a diagnosis of BPD and 10% infants ≤ 24 months at enrollment with HSCHD.

Efficacy results

During the entire study period, there were no cases of RSV hospitalization. Five children were hospitalized and tested for RSV infection during the study, but RSV infection was not detected in any of the children. No deaths were reported in the study.

Safety results

Treatment-emergent adverse events (TEAEs) through 30 days following the last palivizumab injection were reported 22% of subjects, the majority were mild or moderate and considered to be unrelated to study drug.

Treatment-emergent SAEs were reported in 6 subjects, within 30 days of last study drug administration. One SAE of tachycardia paroxysmal was reported as a severe event. One SAE of hemangioma led to discontinuation of treatment.

The observed SAEs, severe TEAEs, or TEAEs leading to study drug discontinuation were not considered treatment related by the investigators.

1.2.2. Discussion on clinical aspects

In this Phase 3b, prospective, non-controlled, multicenter study, evaluating the safety and effectiveness of the liquid formulation of palivizumab in 50 infants at high risk of contracting severe RSV infection in the Russian Federation and the Republic of Belarus between 2016 and 2017, there were no cases of hospitalizations due to RSV. Therefore the primary and secondary outcomes could not be evaluated.

As such, these data on a limited number of subjects does not contribute any news to the already approved indication; there are no new efficacy concerns due to the absence of RSV cases in this small cohort. These results in this mixed population of subjects at risk for serious RSV infection are comparable with results in studies of both lyophilized and liquid formulations in the same indications which were successfully used to obtain marketing approval in numerous countries, and support the approval of the palivizumab liquid formulation in the Russian Federation and the Republic of Belarus.

The formulation of palivizumab was found to be safe and well tolerated in all subjects, consistent with the known safety profile of palivizumab. No new safety signals were identified. Few drug related AE were observed and only considered treatment a single case of SAE related discontinuation was observed, which was not considered related to the treatment.

Rapporteur's overall conclusion and recommendation

Synagis is already approved.

Even in consideration of the obvious limitations, the findings from this observational study seem overall consistent with the established efficacy and safety of palivizumab. The results from study M15-539, 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.

☐ Not fulfilled:

2. Additional clarification requested

Not applicable