

## 1.0 Abstract

### Title

Prospective, non-interventional observation study for the use of palivizumab in high-risk children in Germany – SYNAGIS

### Keywords

Palivizumab, respiratory syncytial virus, high-risk children, hospitalization rate, Germany

### Rationale and Background

Respiratory syncytial virus (RSV) is the most common cause of childhood acute lower respiratory tract infections, and a major cause of admission to pediatric hospitals. The clinical spectrum of RSV-related respiratory diseases is broad and ranges from self-limiting upper airway infections to severe lower respiratory tract infections (LRTI) that may require admission to intensive care unit (ICU). RSV ranks among the top causes of death in childhood from acute LRTI. In Germany, RSV's high contagiousity and its effective mode of transmission results in very high numbers of infected individuals during RSV season, which usually occurs in the cold months between autumn and spring.

Palivizumab (Synagis<sup>®</sup>), a humanized monoclonal antibody against an epitope of RSV envelope fusion protein, has been granted European approval since 1999 for the prevention of serious LRTI in children at high risk for serious RSV disease.

The SYNAGIS Registry was carried out in order to gather comprehensive real-world data on the use of palivizumab in high-risk children. This registry was designed as a post-marketing observational study, and conducted from 2002-2016 with the aim of collecting data on palivizumab administration, the risk factors for a complicated RSV disease, frequency of hospitalizations, and drug adherence. In the course of the years, the registry was amended several times in order to acknowledge changes such as the expansion of the palivizumab label or new scientific information on risk factors for severe LRTI. A detailed overview of the changes is listed in the Appendix.

## Research Question and Objectives

The objectives of this post-marketing surveillance of Synagis<sup>®</sup> were

- To determine Synagis<sup>®</sup> usage patterns in infants under risk for RSV
- To determine RSV hospitalization rates among Synagis<sup>®</sup> infants
- To determine compliance rates among parents of Synagis<sup>®</sup> infants
- To determine Synagis<sup>®</sup> usage in the German healthcare system
- To understand demographics of Synagis<sup>®</sup> infants
- To further evaluate the impact of risk factors

## Study Design

This post-marketing observational study (PMOS) was conducted in a prospective, single-arm, multicenter format in Germany according to the amended protocol dated April 2006.

## Setting

This post-marketing observational study was conducted in Germany. Primary care pediatricians from hospital outpatient facilities and neonatologists from inpatient facilities were invited to participate in this study and enrolled subjects into the registry at their discretion.

## Subjects and Study Size, Including Dropouts

Eligible subjects were infants and children, in whom the attending neonatologist or pediatrician decided to use palivizumab prophylaxis to prevent serious disease due to RSV infection during the current RSV season. These were to be treated according to the German summary of product characteristics (SPC) “Fachinformation” for Synagis<sup>®</sup>.

Summarized over all seasons, data from 30804 subjects was entered into the registry. Of these, 29468 were considered for analysis since they were verifiably treated with Synagis<sup>®</sup> according to the SPC.

## Variables and Data Sources

All study data (baseline characteristics, risk factors, immunoprophylaxis administration) were to be reported on paper-based case report forms (CRF, 2002/03 – 2007/08) or electronic case report forms (eCRF, 2008/09 – 2015/16): Hospitalization details were to be detailed on occurrence on separate hospitalization forms (2002/03 – 2007/08) or within the eCRF system (2008/09 – 2015/16).

## Results

In total, 142723 injections of palivizumab were documented in 29468 evaluable subjects during the observational period. Results of the German SYNAGIS Registry were subdivided into three parts due to procedural changes including changes in the methods of study data reporting during the conduct of the study: (i) seasons 2002/03 – 2006/07, (ii) 2007/08 and 2008/09, and (iii) 2009/10 – 2015/16. Mean age of subjects upon start of immunoprophylaxis with palivizumab was between 4.3 and 5.9 months; there was a slight male preponderance in study participants (53.8%-55.1% males). Median number of palivizumab administrations for all study periods was 5 (range: 1-12). A high proportion of subjects received more than 5 palivizumab injections during the corresponding RSV season (35%-45%).

On the assumption that no multiple RSV-related hospitalization occurred per infant, the RSV-related hospitalization rates were 0.7%-1.6% (according to discharge diagnosis of the treating physician). These rates are still inside the expected margins derived from prospectively randomized trials [1-3].

The decisions of the participating physicians to administer palivizumab prophylaxis to an individual patient were based on underlying risk factors [4], and on the official German recommendations for passive immunization against RSV in neonates: Most evaluable subjects were prematurely born, with a median gestational age at birth between 29 and 32 weeks. A significant proportion (18.9%-42.6%) had CLD (BPD). Medical treatment of CLD in the 6 months preceding the first administration of palivizumab was documented from 2008/09 in 12.5%-14.7% of subjects per study period.

Between 25.2% and 34.9% of subjects were diagnosed with CHD. Hemodynamically significant congenital heart disease (hsCHD) was added to the list of recommended indications for palivizumab in Germany in 2004. Starting in 2008/09, the investigators could indicate whether hsCHD was the main reason for prophylaxis; this was documented in 13%-14.1% of subjects. The overall hospitalization rate for subjects passively immunized with palivizumab and CHD in the German SYNAGIS Registry

2009-2016 was 3.4% (n = 118); the corresponding average number of RSV-related hospitalizations in subjects with CHD diagnosis was 0.8% (n = 26).

The overall compliance/adherence of the parents of evaluable subjects with the palivizumab administration regimen [5, 6] was good in 91.1 – 93.5% of cases (documented per injection commencing in 2008/09 and documented per infant from 2002/03 to 2007/08).

Safety information was documented in the CRFs and by means of separate adverse event reporting forms. Detailed information on adverse events (terms, serious criteria, outcome etc.) were not included in the study database, but were still captured and processed by AbbVie pharmacovigilance. Most frequent events were infections of the respiratory system. Review of the safety data indicates that the majority of the SAEs were not unexpected for the pediatric patients with significant medical conditions (i.e., prematurity, bronchopulmonary dysplasia/chronic lung disease, or CHD) indicated for palivizumab.

## Discussion

This report on the results of the German SYNAGIS Registry comprises one of the largest prospectively documented datasets on children receiving at least one dose of palivizumab during the corresponding RSV season. Notwithstanding, not all infants and children who received palivizumab prophylaxis against LRTI RSV-infection during the observational period could be included in this registry. Therefore, the results presented in this report cannot be used to calculate the real number of subjects on palivizumab prophylaxis in Germany.

The results of the German SYNAGIS Registry confirm the effectiveness of palivizumab prophylaxis in concordance with published reports from other palivizumab registries (recently reviewed by Paes et al. [7]). Despite the lack of comprehensive safety reporting during this registry, the good adherence rates suggest a favorable tolerability profile of palivizumab.

Marketing Authorisation Holder(s)

AbbVie Ltd Maidenhead, UK

Names and Affiliations of Principal Investigators

Prof. Dr. med. [REDACTED]

[REDACTED]  
[REDACTED]

Tel: [REDACTED]

Email: [REDACTED]