Abbott Laboratories (Abbott)

CLINICAL STUDY PROTOCOL

Postmarketing Observational Study (PMOS)

Synagis® Registration

GERM 06-01

Product Name:	Synagis®	
Type of Study:	Postmarketing Observational Study (PMOS)	
Date:	April 2006	
Sponsor:	Abbott GmbH & Co.KG Max-Planck-Ring 2 65205 Wiesbaden	Phone: +49 6122 581168 Fax: +49 6122 582866

This study will be conducted in compliance with this protocol

Confidential Information
No use or disclosure outside Abbott is permitted without prior written authorization from Abbott.

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3 Introduction

Respiratory syncytial virus (RSV) infection presents a worldwide public health burden with seasonal outbreaks lasting from winter through early spring.[1,2,3,4] The peak incidence of RSV illness and hospitalization occurs in infants and young children between two and six months of age[1] with half of all infants infected in the first year of life.[1,2] Approximately 40% of all primary RSV infections in young children give rise to lower respiratory tract infection (RSV-LRTI) primarily comprised of bronchiolitis and pneumonia. There are certain risk factors that have been reported to be associated with an increased incidence of severe RSV disease. Preterm infants both with and without chronic lung disease [(CLD), also known as bronchopulmonary dysplasia (BPD)] are particularly vulnerable to hospitalization due to severe RSV-LRTI. Congenital heart disease (CHD) and low socioeconomic status have been reported as risk factors as well.[1,3,5,6,7]

Treatment options for RSV are limited (e.g. Ribavirin in the past) and therefore most research strategies focus on prevention of severe RSV-LRTI. The successful development of a safe and effective RSV vaccine has been hampered in part due to exaggerated pulmonary reactions, which appeared to be related to active vaccination against RSV. Thus, passive immunoprophylaxis was explored. This passive immunoprophylaxis of high-risk preterm infants, first with RSV IgG-enriched polyclonal immunoglobulin (RSV-IGIV)[8] and subsequently with anti-RSV IgG monoclonal antibody (palivizumab)[8] was found to be safe and efficacious in the prevention of serious RSV LRTI. Palivizumab (Synagis®) is a humanized IgG monoclonal anti-RSV antibody developed by MedImmune Inc (Gaithersburg, MD USA) and marketed internationally by Abbott Laboratories (Chicago, IL USA). Synagis® was approved by the FDA in 1998 and by the European Agency for the Evaluation of Medicinal Products (EMEA) in 1999 for use in high-risk preterm infants to prevent serious RSV LRTI.

Food and Drug Administration (FDA) and EMEA approvals were based on the results of a Phase III prospective multicenter, multi-national, randomized, double blind, placebo-controlled trial (IMpact-RSV), which was conducted during the winter of 1996-1997.[8] Subjects received five monthly intramuscular (IM) injections of Synagis® at a dose of 15 mg/kg or placebo. RSV-related hospitalizations were reduced by 55%, which is both clinically and statistically significant ($p<0.001$). Significant reductions in RSV LRTI severity were also observed in favor of Synagis® recipients as defined by fewer total RSV related hospital days per 100 children ($p<0.001$), fewer total RSV related hospital days with requirement for increased supplemental oxygen ($p<0.001$), fewer total RSV related hospital days with lower respiratory tract infection (LRTI) score ≥ 3 ($p<0.001$), and a lower incidence of intensive care unit (ICU) admissions ($p=0.026$). Adverse events were comparable in the Synagis® and placebo groups. In October, 2003 , Synagis® was approved by the EMEA for the use in children with hemodynamically significant congenital heart disease also.

4 Rationale

With the approval of Synagis® in Germany, an effective prophylactic measure to reduce RSV infection rate in high-risk preterm infants and children with hemodynamically significant congenital heart disease is available. However, there are limited data on the frequency and severity of RSV infections in preterm infants and children with congenital heart disease in Germany and the RSV-related risk factors in the target population. Furthermore there is a need to further evaluate the impact of the german health care system on the treatment with Synagis® .

The Synagis® PMOS will provide information

- when and where the drug is administered,
- how the risk factors are distributed in the investigated population,
- how often RSV-related hospitalization and ICU admission occur, and
- on the compliance rate among parents of Synagis® infants.

Therefore, this observational, non-randomized, longitudinal, cohort study of infants immunized with Synagis® will follow up these infants for the RSV seasons.

5 Study Objectives

The objectives of this post marketing surveillance on Synagis® are:

- To determine Synagis® usage patterns in infants under risk for RSV
- To determine RSV hospitalization rates among Synagis® infants
- To determine compliance rates among parents of Synagis® infants
- To determine Synagis® usage in the german health care system
- To understand demographics of Synagis® infants
- To further evaluate the impact of risk factors

6 Investigational Plan

6.1 Selection of Study Population

The study population will consist of preterm infants and children born with hemodynamically significant congenital heart disease.

Inclusion Criteria

The inclusion criteria are as stated in the German Summary of Product Characteristics (SPC) "Fachinformation" for Synagis® (Appendix I):

- 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 hemodynamically significant congenital heart disease.

Exclusion Criteria

The exclusion criteria are as stated in the German Summary of Product Characteristics (SPC) "Fachinformation" for Synagis® (Appendix I):

- Children with known hypersensitivity to Palivizumab or any component of the formulation, or other humanized monoclonal antibodies.

6.2 Number of Children to be Enrolled

The number of patient's to be enrolled will be app. 1000.

The data for this observational study will be collected from pediatricians in medical practices.

6.3 Investigator Selection Criteria

Each community Pediatrician in care of preterm infants and/or children with congenital heart disease can participate in this study.

6.4 Study Duration

The PMOS will start in autumn 2006 and the cohort of children will be followed throughout the RSV season.

6.5 Study Conduct

This postmarketing observational study will be conducted in a single-arm, multi-center format.

The following data will be documented.

Screening Form

The variables collected on the SCREENING FORM are:

♦ Subject ID, including CRF Number (pre-printed), center (physician) ID and geographic location
♦ Demographic Data
♦ Risk Factors
Details are provided in Section 9, CRF

Synagis Form

The variables collected in the SYNAGIS FORM are:

- ♦ Subject ID, incl. CRF Number (pre-printed), center (physician) ID and geographic location
- ♦ Data of Synagis® injections (including dates, weight, and dose)
- ♦ RSV hospitalization
- ♦ Adverse Reactions
- ♦ Parents' compliance

Hospitalization Form

In order to establish health outcome parameters RSV-related hospitalizations will be recorded on the HOSPITALIZATION FORM. This form will only be used during the RSV season.

The variables collected in the HOSPITALIZATION FORM are:

- Hospital admission dates / length of stay
- Diagnoses and RSV diagnostics
- ICU admission
- Oxygen required
- Mechanical ventilation required

6.5.1 Product Supply

Due to the nature of this study Abbott will not supply any product. The physicians will prescribe the medication for the participants of the study as regulated by section 47 German Drug Law (Arzneimittelgesetz).

7 Adverse Events

7.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal

product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a **serious adverse event (SAE):**

Death of Subject An event that results in the death of a subject.

Life-Threatening An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.

Prolongation of Hospitalization An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.

Persistent or Significant Disability/Incapacity An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as nausea, vomiting, diarrhea, and accidental trauma.

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2 Severity

The physician will use the following definitions to rate the severity for any adverse event being collected as an endpoint / datapoint in PMOS and for all serious adverse events.

Mild The adverse event is transient and easily tolerated by the subject.

Moderate The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event being collected as an endpoint/datapoint in the PMOS and for all serious adverse events, to assess the relationship of the adverse event to the use of Synagis®:

Probably Related An adverse event has a strong temporal relationship to Synagis® or recurs on re-challenge and another etiology is unlikely or significantly less likely.

Possibly Related An adverse event has a strong temporal relationship to Synagis® and an alternative etiology is equally or less likely compared to the potential relationship to study drug.

Probably Not Related An adverse event has little or no temporal relationship to the Synagis® and/or a more likely alternative etiology exists.

Not Related An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to Synagis® or has a much more likely alternative etiology).

If an investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an alternate etiology must be provided by the investigator for the adverse event.

7.4 Serious Adverse Events

7.4.1 Collection Period

All serious adverse events will be reported to Abbott from the time the physician obtains the patient's authorization to use and disclose information until 30 days following the injection of the last dose of physician-prescribed Synagis®.

7.4.2 Reporting

The pertinent legal regulations (German Drug Law, section 29, and section 63b) apply with respect to the procedure for handling adverse drug reactions (ADRs).

In the event of a serious adverse event the physician will notify the Abbott contact person identified below, by faxing the appropriate adverse event forms within 24h of the physician becoming aware of the event.

Any adverse drug reaction that occurs is recorded by the treating physician using a separate "Adverse drug reaction report" form, labeled "Bericht über unerwünschte Arzneimittelwirkung". This form is sent by the treating physician within 24 hours to Uwe Diekmann, Abbott GmbH & Co. KG, Max-Planck-Ring 2, 65205 Wiesbaden-Deleknheim, Phone: 06122/58-1194, fax 06122/58-1628.

8 Ethics and Quality

The German Drug Law defines an observational study as a data collection on routine use of medication, prescribed in the usual manner in accordance with the terms of marketing authorization. The patients/parents must provide authorization to the investigator to use and/or disclosure personal and/or health data before entry into the Synagis® PMOS.

All patient data entered in the patient's case report form will be forwarded – without naming the patient- for evaluation to Abbott GmbH & Co. KG.

The data collection forms inclusive adverse event forms will be checked during data entry for missing or inconsistent data. These data will be completed through the use of data queries, if possible.

9 Case Report Form

Each study center will receive one or more folders with a set of sheets for data collection. The required data should be entered into the data sheets (CRFs) using the institution's measurement procedures. Any observation of an adverse event beginning with the administration of the first dose of Palivizumab must be documented and checked for severity. If it fulfills the severe criterion (SAE) the "Adverse drug reaction report" form, labeled "Bericht über unerwünschte Arzneimittelwirkung" must be completed.

♦ SCREENING FORM

- Patient's initials
- Date of birth (month and year)
- Birth weight
- Sex
- Age at the beginning of the RSV prophylaxis

- Gestational age
- Existence of BPD
- Existence of CHD
- Multiple birth status
- Immune deficiency
- Patient attending daycare
- Children aged 12 years or younger living in the household
- Exposure to secondary smoke
- Family members' history (asthma, allergic rhinitis, eczema)
- Further underlying disease and co-morbidities

♦ SYNAGIS FORM

- Information on whether Synagis® was received last season
- Information on whether start immunization of the current season was in the present hospital
- Information on whether palivizumab prophylaxis was recommended
- Details concerning RSV prophylaxis
- Occurrence of any adverse reactions
- Parents' compliance

♦ HOSPITALIZATION FORM

This form collects data concerning health outcomes, i.e. RSV-related hospitalizations. For each hospitalization during the Synagis® treatment period, the data will be entered in the HOSPITALIZATION FORM.

The following questions regarding any RSV-related hospitalization will be asked:

- Subject ID
- Date of hospital admission
- Date of hospital discharge

- Diagnoses at time of hospital discharge
- Performance of an RSV test and result
- Requirement of ICU admission
- Requirement of supplemental oxygen
- Requirement of mechanical ventilation

Note:
RSV infections are not Adverse Events as they are expected in a number of children and because the infection rate with RSV serves as a parameter for the PMOS outcome.

Other infections and reasons for hospitalization must be recorded on the AE Form.

10 Data Analysis Plans

Basic data analysis parts are

- demographic data (sex, gestational age, birth weight; frequencies, statistics). Gestational age and birth weight will also be classified in order to identify premature birth (gestational age $\leq$ 35 weeks) or low weight (<2000 g). These categories are in addition to the risk assessment and need not necessarily be identical.
- risk for RSV infection (frequencies):
  1. premature birth
  2. BPD
  3. congenital malformation
  4. multiple birth
  5. immuno-deficiency
  6. attending daycare
  7. children <12 years in the household
  8. smoking in the family
  9. family history of asthma

10. family history of allergic rhinitis
11. family history of allergic eczema
12. other reasons. If other reasons are given, no analysis will be conducted.

- immunization data
    1. variables on history and rationale for the immunization (frequencies)
    2. age at start of prophylaxis (statistics) and month of start of prophylaxis (frequencies), assuming that the first entry is done for the start immunization
    3. number of follow-up administrations depending on the start of prophylaxis (frequencies). From this analysis the "compliance" may be concluded, assuming a need for a monthly follow-up administration in the season from September to May, i.e. if the prophylaxis was started in December a "regular" schedule would lead to 5 follow-up administrations.
- hospitalization data: Hospitalization is interpreted as efficacy parameter.
    1. number of hospitalizations (frequencies): For each hospitalization, a separate form is to be filled in.
    2. diagnosis of infection (stated at dismission): 5 different diagnoses and an "other" field will be analyzed for their frequencies.
    3. outcome of an RSV test (frequencies)
    4. complications in terms of need for intensive care, oxygen or mechanical respiration. The analysis will comprise frequencies as well as the duration (if documented).

All analyses will be done descriptively; no statistical tests are planned for this PMOS.

11 Final Report and Publications

On the basis of the analysis an Integrated Final Report is generated according to Abbott SOP Q-12-06-001.

12 References

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ABBOTT LABORATORIES
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Approved by:

Signature	Date