SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Synagis. This scientific discussion has been updated until 1 October 2004. For information on changes after 1 October 2004 please refer to module 8B.

I SCIENTIFIC DISCUSSION

1. Introduction

Synagis (MEDI-493, palivizumab) is a humanised monoclonal IgG1κ antibody developed from a murine monoclonal antibody (Mab) - originally discovered by the NIH - directed against the antigenic site A on the fusion or F protein of respiratory syncytial virus (RSV). It is produced as a lyophilised powder intended to be reconstituted with water for injections to 100 mg/ml prior to intramuscular (IM) administration.

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.

2. Part II: Chemical, pharmaceutical and biological aspects

Synagis is presented as a sterile lyophilised powder in single-dose vials containing either 50 mg or 100 mg of palivizumab.

Palivizumab was derived from a murine monoclonal antibody and humanised by grafting of the complementarity determining regions (CDR) of the murine monoclonal antibody Mab 1129 into a human antibody framework with an IgG1 constant region. It is composed of two heavy and two light chains of a total molecular weight of approximately 148,000 Daltons and has been extensively characterised. The production cell line is a well-established murine myeloma NS0 cell line.

All stages of antibody production from cell culture to harvesting, purification, formulation, filling and lyophilisation take place at Boehringer Ingelheim Pharma KG, Germany.

Composition

The composition of the product for the 50 mg and 100 mg palivizumab vials is given below:

Composition :					
Active ingredients	**mg/ml (after recon)**	**50 mg vial**	**100 mg vial**	**Function**	**Standards**
Palivizumab	100	73 mg	122 mg	Active	In-house
Other ingredients					
Glycine	0.2	0.16 mg	0.27 mg	Stabiliser	Ph. Eur.
Histidine	7.3	5.2 mg	8.7 mg	Stabiliser	Ph. Eur.
Mannitol	56.3	40.5 mg	67.5 mg	Bulking agent	Ph. Eur.

Prior to use, the product is reconstituted with Water for Injections to give a sterile, aqueous, 100 mg/ml solution, for administration by intramuscular injection. The reconstituted product also contains 3.0 mM glycine, 47 mM histidine and 5.6% mannitol. Palivizumab will be packaged with a 1 ml ampoule of Water for Injections, Ph. Eur.

The product is presented in a Type I (Ph. Eur.) 4 ml capacity (50 mg) or 10 ml capacity (100 mg) glass fliptop vial, closed with a siliconised, butyl rubber, lyophilisation stopper. The stopper is covered by an aluminium cap or equivalent.

Two formulations of palivizumab were used in clinical trials; a solution formulation (early clinical trials) and the lyophilised product which is the one proposed for marketing and the subject of this application.

Product development and finished product

Development pharmaceutics

Formulation studies were performed to develop a suitable base for palivizumab lyophilisate in order to enhance the solubility without resulting in aggregation, and have good stability and processing characteristics. The composition of the formulation buffer comprises 25 mM histidine with 1.6 mM glycineA 3-4% concentration of mannitol exhibited superior cake characteristics and reconstitution properties. To ensure that the withdrawable contents of the vial are not less than the label claim, an overfill has been added to each vial. Therefore upon reconstitution to a 100 mg/ml solution, the volume of the product will be 0.7 ml for the 50 mg vial or 1.2 ml for the 100 mg vial.

Method of preparation

The maximum batch size is approximately 45,000 vials for the 100 mg presentation and 93,000 vials for the 50 mg presentation. The manufacturing process is a standard sterile filtration followed by lyophilisation. In-process controls are: testing of samples for fill volume and integrity testing of sterilisation filters. Validation is performed according to standard procedures.

Control of starting materials

The active substance is formulated and provided as an aqueous solution containing 54 mg/ml palivizumab, 25 mM histidine, 1.6 mM glycine and 3% mannitol.
Routine testing includes total protein, biological potency, identity, size exclusion chromatography, endotoxins, sterility and process impurities.

Development genetics
The generation of the recombinant cell line expressing palivizumab involved a series of major steps which included the production and selection of murine monoclonal antibody Mab 1129, the humanisation of Mab 1129, and the construction and selection of the expression myeloma NS0 cell line.

Cell bank system
Twenty one candidate production cell lines were evaluated for growth rate and secretion of antibody. Selection of one cell line, suitable for large-scale production, was based on expression level, growth rate, and stability. The best candidate after cloning resulted in the generation of the Accession Cell Bank (ACB). Cells from one ACB vial were used to establish the Master Cell Bank (MCB). Each MCB vial can be used to prepare a Working Cell Bank (WCB).

The MCB was characterised for identity, quality and safety measuring the following parameters:
mouse antibody production, isoenzyme analysis, in vivo assay for adventitious viruses, in vitro assay for adventitious viruses, sterility, mycoplasma, extended S+L- focus assay, extended XC plaque assay, DNA profiling, cDNA sequences of H & L chains, and copy number.

The WCB was characterised for sterility, DNA-fingerprinting, mycoplasma and in vitro assay for adventitious viruses. No evidence of microbial contamination was found. The DNA profile was characterised and the profile was found to be similar to that of the MCB.

Fermentation and harvesting

The production batch size for palivizumab is approximately 10,000 litres. There are two parts of the fermentation process, the T-Flask and spinner culture in which the volume of the WCB is increased and the bioreactor process where the volume is increased through stages to the final volume of 10,000 litres. The cells and debris are removed from the culture, and the pH and conductivity of the resulting cell-free conditioned medium are adjusted for further processing.

Purification

The palivizumab purification process consists of several viral removal/inactivation steps.

Characterisation

Palivizumab specifically binds with high affinity (Kd = 0.96 nM) to the F protein of respiratory syncytial virus (RSV) and has been isotyped as an IgG1 with a molecular weight of approximately 148, 000 Daltons as measured by MALDI-TOF mass spectrometry. It is composed of two heavy chains and two light chains as determined by reducing SDS-PAGE and the molecule has an isoelectric point of greater than 9 as determined by IEF.

Analytical Development

SDS PAGE and RSV Microneutralisation - used during development - have been validated.
Validation of total protein assay, biological potency, identity, size exclusion chromatography and methods used to detect impurities has been performed.

Detailed information on the palivizumab reference standards has been provided. The characterisation of the reference standard encompasses a series of analytical tests to confirm that the structural identity and biological activity is consistent with the set criteria.

Process validation

Process validation studies were performed on:

- comparability of palivizumab produced at different scales (up to 10000 L),
- comparability of palivizumab manufactured at MedImmune and Boehringer Ingelheim,
- cell culture development studies,
- bioreactor process assessment summary of results,
- validation of bulk drug manufacturing process,
- validation studies for the purification process,
- validation of removal of process contaminants.

Control tests on the finished product

Routine testing on the finished product includes appearance of the lyophilised powder and reconstituted solution, pH, moisture, total protein, biological potency, identity, size exclusion chromatography, endotoxins, sterility and uniformity of content

Stability

Based on the presented stability data a storage time for the active ingredient of 6 month at 2-8 °C is acceptable. The proposed storage time for the finished product 2-8° C for 2 years can be accepted provided that real time stability data on an on-going basis is provided.
The Marketing Authorisation Holder applied for extension of the shelf-life of the finished product. Based on the provided data the variation applied was accepted. The currently approved shelf-life is as stated in the SPC.

Viral safety

The virological safety of the product is considered satisfactory since palivizumab is a recombinant DNA monoclonal antibody produced in well-established cell lines, the purification process includes several virus removal/inactivation steps.

Steps of the manufacturing process were evaluated for their capacity on virus removal/inactivation: The virus validation studies were performed with the Murine Xenotropic Type C Retrovirus (retrovirus), Pseudorabies virus (PRV), human Poliovirus type 1 (polio-1) and Simian Virus 40 (SV-40). The retrovirus was selected as the model virus for type A and C retroviral particles found in the cell bank. PRV, polio-1 and SV-40 were selected as unspecific model viruses consisting of one enveloped DNA virus and two non-enveloped viruses of the RNA and DNA genome type.
Medium components were either recombinant products (amino acids and vitamines, recombinant human Insulin) or were derived from bovine material (BSA, Transferrin, lipoprotein fraction). Bovine derived components were made from plasma sourced in US or Canada which are free of BSE.
The Company has agreed to submit follow-up information on an ongoing basis.

3. Part III: Toxico-pharmacological aspects

RSV is a pleomorphic virus, a member of the family of Paramyxoviridae, comprising a single strand, sense-negative RNA genome, which is tightly associated with viral protein to form the nucleocapsid. RSV is comprised of two major groups (A and B). The RSV genome codes for 3 transmembrane surface proteins (F; G and SH), 2 matrix proteins (M and M2), 3 nucleocapsid proteins (N; P and L) as well as for 2 non-structural (NS1 and NS2) proteins. The surface fusion (F) and attachment (G) proteins are the only viral components inducing RSV neutralising antibodies.

The F protein, a 70 kilodalton disulphide linked heterodimer, mediates fusion of the viral envelope with the plasma membrane and syncytium formation; has a high degree of genetic and antigenic homology between RSV group A and RSV group B; and has been antigenically stable over years. Antibody against the F protein neutralises both RSV group A and B isolates.

Immunity against RSV is mediated via humoral and cellular effectors, including serum antibodies, secretory antibodies and MHC class I restricted cytotoxic T-cells. In general, humoral immune responses involving secretory and serum antibodies appear to protect against infection of the upper and lower respiratory tract, while cell-mediated responses directed against internal viral proteins appear to be active against the manifested infection. RSV replicates primarily in the respiratory epithelium. For this reason, high titres of serum neutralising antibodies have been shown by animal studies and by clinical trials with an RSV hyperimmune globulin (Respigam) to protect the lower respiratory tract against RSV infection. This hyperimmune globulin has to be administered intravenously, due to the lower anti-RSV titre and the resulting larger volume, whereas palivizumab, which is more potent than the hyperimmune globulin, can be administered intramuscularly.

Pharmacodynamics

Palivizumab binds to the F-Protein of RSV and the kinetic constants for the association and dissociation of the humanised and the chimeric form of Mab 1129 are comparable, ranging from a Kd of 0.7 - 0.98 nM for the humanised and 1.0 - 1.7 nM for the chimeric form of palivizumab.

The ability of the humanised and the chimeric forms of the murine Mab 1129 to inhibit the replication of RSV in vitro were studied by a modified microneutralisation or a microneutralisation assay. Furthermore palivizumab was studied in comparison to a RespiGam against RSV.

Palivizumab and RespiGam were further tested to inhibit the in vitro replication of recent clinical isolates of RSV from US origin (n=57) or 20 clinical isolates of RSV from Europe (UK, 14; Spain, 4, Sweden, 2) measured by a F-protein specific ELISA. Neutralisation was defined as a 50% reduction of the O. D. values in the F-protein ELISA, between the wells with and without palivizumab. 2/20 of the isolates could not be grown, 57/57 of the US- and 18/20 of the EU-isolates fulfilled the definition of neutralisation by palivizumab.

A direct comparison of the activities of two humanised RSV Mabs palivizumab and RSHZ19 was performed. RSHZ19 is also IgG1, kappa monoclonal antibody directed to a specific neutralising

epitope of the F protein of RSV which was proved unsuccessful in pivotal trials and was discontinued. The comparison was assayed by RSV Microneutralisation Assay, RSV Fusion Inhibition Assay, BIAcore Analysis and the Cotton Rat Prophylaxis Model. The results indicated that palivizumab is approx. 5 times more potent than RSHZ19 and 20 times more potent than RespiGam in the microneutralisation and in the fusion inhibition assay. In vivo potency was determined in the cotton rat model where palivizumab was 2.2- 3.5 (depending on the virus strain; Long or B18537) times more potent than RSHZ19 to achieve a 100-fold reduction of the RSV titre in the lungs of infected animals.

In vivo, palivizumab was evaluated for the ability to reduce virus titres in the lung during an ongoing infection in the cotton rat model. Palivizumab was able to reduce the virus titres in the lungs when applied prophylactically or as a treatment for an ongoing infection from approx. 105 to 102 Pfu/gram lung at concentrations of 5 mg/kg after either IM or IV administration. At the concentration of 5mg/kg the virus titres of group A as well as group B strains of RSV were >99% reduced. Prevention of the formation of histopathological changes in the lung was a further parameter studied, indicating the efficacy of palivizumab.

In several studies in the cotton rat model no indications for the occurrence of antibody dependent enhancement of infection by the treatment with palivizumab were detectable.

Pharmacokinetics

Single dose pharmacokinetic studies of palivizumab in Cynomolgus monkeys (n= 2)determined by pharmacokinetic analysis of plasma samples revealed that the distributional phase or α- half-life of palivizumab was 8.8-12.6 hours, while the elimination phase or β-half-life was approximately 8.6 days.

Three groups (2 animals per group, one of each sex) of cynomolgous monkeys were either administered PBS, 10 mg/kg or 30 mg/kg of palivizumab intravenously within a 15 minute period on day 1. These dosages provided mean cmax concentrations of 286 and 595 µg/ml respectively, approximately 10 and 20 times the effective concentration (30 µg/ml) in the cotton rat model.

Considerable variability was noted in the biphasic half-life of the drug in the cotton rat model, with the α-phase lasting from 0.24 hours to 30.66 hours; the β- phase was more prolonged, lasting from 4.2 days to 5.9 days. No influence on the serum levels of palivizumab by a RSV infection could be detected in cotton rats.

Toxicity

Single dose toxicity
A single dose toxicity study of palivizumab administered to Sprague Dawley rats via intravenous injection including assessment of clinical signs, body weight changes, food consumption, ophthalmoscopy, haematology, clinical and anatomic pathology until 14 days post injection gave no indication of toxicity or statistically significant deviations from normal caused by the test article for the described parameters. These results could be confirmed in Cynomolgus monkeys after a single administration of palivizumab.

Repeated dose toxicity/ reproduction toxicity/ mutagenicity/ oncogenicity/carcinogenicity/ ecotoxicity
Studies on repeated dose toxicity, effects on the reproduction, embryo-foetal & perinatal toxicity, mutagenic potential, oncogenic/carcinogenic potential and ecotoxicity/environmental risk assessment were not considered necessary by the applicant and were not performed.

The lack of repeated dose toxicity studies (including reproductive toxicity) was justified by the company by the immunogenicity of the human compound in animals and the lack of binding of the compound to a range of tissues. In the initial preclinical safety study conducted in cynomolgus monkeys one animal showed a xenogeneic antibody response (antibody against the human portion of palivizumab). It was believed that repeat dosing in animals would represent a different response than

an anti-idiotypic response that may be seen in humans. However, the ensuing clinical studies have not revealed significant toxicity problems related to repeated dosing.

Local tolerance

Local tolerance was evaluated in a study in New Zealand White rabbits in which microscopic evaluation of the injection sites of the animals gave no indication for significant treatment related effects attributable to the test article.

Cross reactivity

The applicant stated in the preclinical expert report that since the product is indicated only for use in infants there is no need to evaluate the potential toxicity of palivizumab on the reproduction. Therefore a cross-reactivity study according to the Note for *Guidance Production and Quality Control of Monoclonal Antibodies* with tissue from children of both sexes was performed. No binding was observed in any of the tested human tissues.

Immunogenicity

Palivizumab was immunogenic in Cynomolgus monkeys and led to the generation of anti-palivizumab antibodies in the low dosage- as well as in the high dosage group in 1/4 animals. In all animals at the time of determination of the amounts of anti-palivizumab-antibodies, high amounts of palivizumab were present in the samples. This observation makes the immunogenicity findings even more important, since the assay system for the detection of anti-palivizumab-antibodies or HAHA lacks the ability to detect anti-palivizumab-antibodies in the presence of high amounts of palivizumab. Despite the inhibition of detection of anti-palivizumab antibodies by soluble palivizumab the assay is qualitatively useful in detecting anti-palivizumab activity.

4. Part IV: Clinical aspects

Human respiratory syncytial virus (RSV) is a common human respiratory tract pathogen and is the major cause of severe lower respiratory tract illness in young children world-wide. It outranks all other microbial pathogens as a cause of pneumonia and bronchiolitis in infants under 1 year of age. It is estimated that 50-70% of all infants experience RSV infection in the first year of life. RSV is estimated to cause 60-90% of the paediatric hospitalisations for bronchiolitis in Europe and up to 50-90% in the US. Particularly severe cases are seen in 'high risk' patients i.e. premature infants, children with bronchopulmonary dysplasia (BPD) and those with congenital heart disease (CHD).

In the Northern Hemisphere, the RSV season typically commences in November and lasts through April, but RSV activity may begin earlier or persist later in a community.

Pharmacodynamics

Palivizumab was derived from the murine monoclonal antibody 1129 and humanised by grafting the complementarity determining regions (CDR) into a human antibody framework with an IgG1 constant region. Prior to the initiation of clinical trials, preclinical studies demonstrated that palivizumab had potent RSV neutralising and fusion-inhibitory activity. Both microneutralisation and plaque reduction neutralisation assays were utilised to evaluate the in vitro antiviral properties of 1129 or palivizumab. The plaque reduction assay was used to evaluate the neutralisation of either A (Long) or B (18537) strains of RSV. Palivizumab neutralised both types of RSV in a dose dependent manner.

A total of 77 clinical RSV isolates evaluated by the neutralisation assay were shown to be neutralised by palivizumab, 57 of these were obtained in the USA consisting of 34 A and 23 B subtype isolates. Further, the reactivity of palivizumab with isolates passaged in vitro was evaluated using an immunofluorescence assay (IFA). Laboratory isolates collected throughout the 1996-1999 RSV seasons and fresh nasal specimens from RSV-infected infants in Belgium, Denmark, Finland, France, Germany, Greece, Netherlands, Spain, Sweden, Switzerland, and the United Kingdom were obtained. In total 389 strains were collected and all were recognised by and bound by Synagis. Additionally,

96 strains from the United States and 6 from Uruguay were also tested by IFA and without exception all isolates reacted with Synagis. Thus, the binding activity of Synagis using IFA against a panel of 491 clinical and laboratory strains of RSV isolated between 1996 and 1999 from different geographical regions have demonstrated binding of Synagis to the epitope. These data indicate that the epitope site to which Synagis binds is highly conserved over time and across geographic regions.

In the cotton rat model, pre-treatment with palivizumab was shown to reduce mean pulmonary viral titres (replication) by 99% at serum concentrations of approximately 30 µg/ml, and was selected as the target C_{trough} serum level for the phase I/II studies. Viral replication, pulmonary inflammation or histopathology was not enhanced at any of the palivizumab concentrations examined. In these in vivo tests, palivizumab was 50-100 fold more potent than RespiGam,. In addition, no RSV mutants escaped therapy, and re-infection with RSV after palivizumab exposure did not enhance RSV viral titres (replication). As a correlate to the cotton rat data, palivizumab at a dose of 15 mg/kg has been demonstrated to decrease pulmonary RSV titres in tracheal secretions in paediatric patients who were hospitalised and intubated secondary to severe RSV infection. These data provide evidence for the anti-RSV activity of palivizumab at the primary site of pathology in humans, the lung. Treatment of children with 15 mg/kg palivizumab was associated with a statistically significant one-log reduction of RSV titres in tracheal secretions as compared to controls (p=0.004).

Pharmacokinetics

Two formulations of palivizumab were used; a sterile liquid formulation in phosphate buffered saline and a lyophilised product for reconstitution in sterile water. The liquid preparation was only administered IV, while the lyophilised product was administered both IV and IM. In the majority of the prophylaxis trials the lyophilised product proposed for commercialisation was used. Both forms of the product delivered similar 30 days trough palivizumab levels, and the safety profiles were indistinguishable.

PKs were evaluated in healthy adults and in high-risk infants. The results obtained are comparable with those known for other chimeric monoclonal antibodies except for the median terminal half-life, which is unusually high for such a product. Whether administered IV or IM palivizumab demonstrated an elimination half-life of 18 days (mean) in adults and 20 days in children. Palivizumab has a time to maximum serum concentration of 1.6 hours given IV and 5 days given IM. The mean apparent volume of distribution is 57 ml/kg. In children, monthly IM doses of 15 mg/kg achieved mean 30 day trough serum concentrations of approximately 40 µg/ml after the first injection, 60 µg/ml after the second injection, and 70 µg/ml after the third and fourth injection throughout the RSV season. The 15 mg/kg dose given every 30 days was selected based upon preclinical models of RSV lung infection and the PKs obtained in the phase I/II studies assured C_{trough} levels at or above the 30 µg/ml target level. This level was initially demonstrated to be effective in the cotton rat model. Palivizumab was safe and well tolerated at doses up to 30 mg/kg, the maximum dose studied.

Clinical trials

The clinical programme consists of 16 completed studies including studies in healthy adult volunteers. These trials include 5 trials in support of the efficacy and safety of palivizumab in RSV disease and 5 additional studies in support of the safety of palivizumab. Some patients treated in the pivotal phase III study were given palivizumab for a second season as part of an open-label phase IIIb study.

Overall the clinical study programme included 62 healthy adult volunteers and 1797 children in the primary paediatric prophylaxis and treatment studies and 21 bone marrow transplant patients. Additionally, 56 children were assessed during a second season of prophylactic use of palivizumab. Overall, 1344 patients were enrolled to receive palivizumab (1282 children and 62 adults) and 575 patients were enrolled to receive placebo.

Phase I/II studies evaluated the dose finding and the mode of administration (IV vs. IM). Additionally, the use of palivizumab in the treatment of RSV was evaluated. The treatment studies suggested that

despite reduction of viral titre in the lung the severity of RSV disease was not significantly altered, and thus only prophylaxis indication was evaluated in the phase III studies.
The pivotal study (MI-CP018, The IMpact RSV Study) was a multi-centre, randomised, double blind, parallel group, placebo controlled trial conducted during the winter of 1996-1997. The trial evaluated the safety and efficacy of palivizumab in preventing hospitalisation related to RSV infection in high-risk infants. These were children with BPD (who were less than 2 years of age and had required therapy for BPD within 6 months of study entry) or with premature gestation ($\leq$35 weeks of gestation and $\leq$6 months of age at study entry). The patients were to receive five monthly IM injections of palivizumab at a dose of 15 mg/kg or matching placebo and were followed for 150 days or 30 days after the last scheduled injection. The study was conducted at 119 centres in the USA, 11 centres in the UK and 9 centres in Canada. 1502 children were randomised, 500 into the placebo group and 1002 into the palivizumab group.

The groups were balanced at entry with regard to demographic and RSV risk factors with no differences between the groups in terms of sex, race, enrolment or birth weight, mean gestational age, age at enrolment, history of previous RSV infection, or baseline RSV neutralising antibody titre. Approximately half (50.7%) of the children met the entry criteria for BPD and half met the entry criteria for prematurity (49.3%). The mean gestational age was 29 weeks and the mean birth weight was 1261 g.

Study	Study Design	Subject/Patient Population	Dose	Patients Enrolled* MEDI-493/Placebo
Phase I: Healthy adults				
MI-RSV-9401a	Phase I Open label	Healthy Adults	1 mg/kg IV single infusion	4/0
MI-RSV-9401b	Phase I Open Label, Dose escalation	Healthy Adults	3, 10, 15 mg/kg IV single infusion	12/0
MI-RSV-9401c	Phase I Open Label, Dose escalation	Healthy Adults	3, 10, 15 mg/kg IV q30 days for 2-3 doses	12/0
MI-CP007	Phase I Open Label	Healthy Adults	3 mg/kg IM q30 days for 2 injections	4/0
MI-CP017	Phase I Open Label	Healthy Adults	15 mg/kg IV single infusion	6/0
MI-CP035	Phase I Open Label Dose escalation	Healthy Adults	15, 30 mg/kg IV single infusion	12/12
Phase I/II: Paediatric Prophylaxis (Prematurity, BPD)				
MI-CP005	Phase I/II Double-blind Placebo-controlled, Dose escalation	High risk children	3, 10, 15 mg/kg IV q30 days for up to 5 infusions	42/20
MI-CP011	Phase I/II Open Label Dose escalation	High risk children	5,15 mg/kg IM q30 days in US; 15 mg/kg in Panama; 10 mg/kg IM q30 days in Costa Rica for up to 5 injections	65/0
MI-CP012	Phase I/II Open Label Dose escalation	High risk children	5, 15 mg/kg IM q30 days for up to 5 injections	60/0 (Australia, New Zealand, South Africa)

Phase III: Paediatric Prophylaxis (Prematurity, BPD)				
MI-CP018	Phase III Double-blind Placebo-controlled	High risk children	15 mg/kg IM q30 days for 5 injections	1002/500 (US, UK, Canada)
MI-CP036	Phase IIIb Open-label	High Risk children from CP018 (second season)	15 mg/kg IM q30 days for 5 injections	88 (32 first season, 56 second season)

Phase I/II: Paediatric Treatment (Children with RSV)				
MI-CP009	Phase I/II Double-blind, Placebo-controlled, Dose escalation	Children with RSV (Treatment)	5, 15 mg/kg IV single infusion	30/30 (24 in USA) (36 in Panama)
MI-CP013	Phase I/II Double-blind Placebo-controlled, Dose escalation	Children with RSV (Treatment)	5, 15 mg/kg IV single infusion	7/7 (Australia, New Zealand, South Africa)
MI-CP026	Phase I/II Double-blind Placebo-controlled	Children with RSV (Treatment)	15 mg/kg IV single infusion	17/18
Phase I: Bone marrow transplantation				
MI-CP034	Phase I	Bone marrow transplant or stem cell transplant recipients with RSV infect.	15 mg/kg IV single infusion	15/0
MI-CP004	Phase I	Bone marrow transplant recipients	15 mg/kg IV single infusion	6/0

*unless otherwise noted, patients or subjects were in the USA.

Efficacy

Efficacy endpoints

Primary endpoint of efficacy:
Incidence of hospitalisation due to RSV infection

Secondary efficacy parameters:

a. total days of hospitalisation from RSV infection
total days of RSV hospitalisations requiring increased supplemental oxygen
total days of RSV hospitalisation with a moderate or severe lower respiratory tract infection (LRI score ≥3)
incidence and total days of RSV-associated ICU stay
total days of RSV-associated mechanical ventilation

b. incidence and total days of hospitalisation for non-RSV respiratory disease, any respiratory disease and hospitalisation for any cause
incidence of otitis media

All but 1% of the children completed the study in that they reached the primary endpoint of RSV related hospitalisation or were followed for 150 days without reaching the endpoint. Approximately 93% of children received all 5 scheduled doses of study drug.

Palivizumab at monthly IM doses of 15 mg/kg reduced RSV related hospitalisations by 55% which is both highly clinically and statistically significant ($p<0.001$). This equals an absolute risk reduction of 5.8%, which means that the number needed to treat is 17.2 to avoid one hospitalisation.

Table 1. Summary of Clinical Efficacy for Palivizumab				
Parameter	Rates		% Reduction	*P* Value
	Placebo	Palivizumab		
Incidence of RSV hospitalisation, %	10.6	4.8	55	<.001
RSV hospitalisations/100 children, day	62.4	36.4	42	<.001
O_2 requirement/100 children, day	50.6	30.3	40	<.001
Incidence RSV ICU care, %	3.0	1.3	57	.026
ICU/100 children, day	12.7	13.3	—	.023
Mechanical ventilation, %	.2	.7†	—	.280
Mechanical ventilation, total number of days	1.7	8.4	—	.210
All respiratory hospitalisations, %	22	16	27	.008
Respiratory hospitalisations/100 children, day (including RSV)	180	124	31	.004
Otitis media, %	40	42	—	.505
Deaths, %	1	.4	—	.169

† Includes 3 infants who required prolonged ventilatory support.

Subgroup Analyses of RSV Hospitalisation by Treatment Group*				
Group	Rate, %		% Reduction	*P* Value
	Placebo	Palivizumab		
All infants	10.6	4.8	55	.00004
Premature infants with CLD	12.8	7.9	39	.038
Premature infants without CLD	8.1	1.8	78	<.001
Neonatal Weight				
>5 kg	10.7	5.2	51	.014
<5 kg	10.5	4.5	57	.001
Neonatal gestational age				
<32 wk	11.0	5.8	47	.0026
32-35 wk†	9.8	2.0	80	<.001

* CLD indicates chronic lung disease.

† Rates for infants (*N*=355 total) born at 32 to 35 weeks of gestation, but without CLD, were 10% and 1.8% for placebo and palivizumab recipients respectively.

Children receiving all five palivizumab injections showed a 62% reduction in RSV hospitalisation. Hospitalisation rate due to the number of palivizumab injections is shown in the following tables:

	Placebo N=500		Synagis N=1002		
Study drug dose	Number of RSV hospitalisations		Number of RSV hospitalisations		Reduction
1	9	1.8%	12*	1.2%	33%
2	16	3.2%	16	1.6%	50%
3	18	3.6%	13	1.3%	64%
4	6	1.2%	7	0.7%	42%
5	5	1.0%	2	0.2%	80%
Total	54	10.8%	50	5.0%	54%

*The 12 hospitalisations after study dose #1 for the Synagis group does not include the first RSV hospital admission for one patient, who was hospitalised after randomisation but before receiving Synagis

RSV hospitalisations after initial dose

Day after 1st dose of study drug	Placebo N=500		Synagis N=1002		Reduction
0-4	0	0.0%	3	0.3%	None
5->30	9	1.8%	9	0.9%	50%

A significant reduction in RSV related hospitalisation was observed in both premature infants ($p<0.001$) and children with BPD ($p=0.038$). The direction of the treatment effect was consistent over time during the RSV season, across countries participating in the trial, and within subgroups of children defined by gender, entry age, gestational age, entry weight, and race/ethnicity. Significant reductions were also observed in favour of palivizumab recipients for total RSV related hospital days, total RSV related hospital days with requirement for increased supplemental oxygen, total RSV related hospital days with LRI score $\geq$3, and incidence of ICU admission. The degree of reduction in total days of RSV hospitalisation (41%) was less than the degree of reduction in the incidence of RSV hospitalisation (55%). Palivizumab did not reduce the severity of the disease in children hospitalised due to RSV infection. It did not affect the severity of RSV disease in terms of total days of ICU stay and mechanical ventilation per 100 randomised children. These numbers were slightly – but not significantly- greater in the treatment group as presented in Table 1. The increased rates for ICU/100 children (days) and those for mechanical ventilation (% total number of days) in the palivizumab group are mainly due to the values of three children with severe underlying illnesses which in turn account for 60% of the ICU days and 65% of the MV days. The severity of the RSV disease can therefore be viewed as a reflection of their severe underlying pulmonary disease and not as an enhancement of the disease by palivizumab. There was also a significant reduction in the overall incidence of hospitalisation for any cause (30.6% placebo vs. 24.4% palivizumab, $p=0.011$). In the placebo group, RSV related hospitalisations represented 34.6% of all hospitalisations as compared to 19.7% for the palivizumab group. Palivizumab also reduced the incidence of all respiratory hospitalisations but did not reduce the incidence of respiratory hospitalisation not attributable to RSV (14.4% placebo vs. 13.0% palivizumab, $p=0.470$).

The efficacy of palivizumab was assessed with regard to the facts that RSV is the most common cause of LRI in infants, especially in those of premature gestation and BPD and that serious RSV disease is the primary cause of rehospitalisation of these infants. The reduction of the RSV hospitalisation rate by 55% and the reductions in all secondary endpoints except those with low frequency i.e. MV and ICU (days) provide medically significant evidence of efficacy. Thus, over half of the children who normally are hospitalised due to severe RSV infections were spared hospitalisation, the complications of a severe disease course and the stress of subsequent treatment regime.

Children less than two years of age and with haemodynamically significant congenital heart disease

Children with haemodynamically significant and surgically uncorrected congenital heart disease (CHD) are at particularly increased risk for contracting severe infection with Respiratory Syncytial Virus (RSV). A multi-centre prospective study in the late 1980's showed that children with CHD had a three-fold higher mortality, significantly longer hospitalisations, and increased oxygen requirements relative to children without CHD (Navas et al. J. Pediatr. 1992; 121:348).

Protective immunity to RSV infection is correlated with levels of neutralising serum antibodies above certain threshold titres and wanes with decline in e.g. passively transferred maternal antibodies. The administration of RSV specific polyclonal immunoglobulin (RSV-IVIG) has previously been demonstrated to prevent disease in premature children and in children with chronic lung disease. However, severe safety problems were observed in the group of children with CHD, specifically in children with cyanotic CHD. It was later hypothesised that the increased rate of SAE in this patient group could be ascribed to volume overload and/or increased blood viscosity due to high immunoglobulin protein load. Consequently, special attention has been paid to the safety and efficacy of future pharmacological products intended for this very fragile patient group.

In November 1998 the study MI-CP048 was initiated as a U.S. post-marketing commitment to evaluate the safety of palivizumab in children less than 2 years of age with CHD. Initially 248 children were randomised, but the sample size was extended to include 1280 children and RSV hospitalisation was added as primary (efficacy) endpoint of the trial. This data was used to broaden the indication in the EU.

MI-CP048 was designed as a phase III, double blind, placebo-controlled, multi-centre, international trial with the objective to assess safety and efficacy of palivizumab in children with CHD.
The Study included 76 sites in the U.S., Canada, France, Germany, Poland, Sweden and the UK.

Clinical Efficacy:

Outcomes/endpoints
The primary endpoint of Study MI-CP048 was the reduction of the incidence of RSV hospitalisations among children with haemodynamically significant CHD when compared to placebo. This endpoint was identical to that used in the initial pivotal trial MI-CP018 used to license palivizumab worldwide. The primary safety endpoint was to describe the safety and tolerance of palivizumab compared with placebo.

Secondary endpoints included
1. RSV hospitalisation outcomes as measured by total days of RSV hospitalisation per 100 randomised children.
2. Total RSV hospital days with increased oxygen requirement per 100 randomised children
3. Incidence and total days of RSV-associated intensive care per 100 randomised children.
4. Incidence and total days of RSV-associated mechanical ventilation per 100 randomised children.
5. The effect of cardiac bypass on serum palivizumab concentrations.
6. Palivizumab trough concentrations before the second and fifth doses.

RSV hospitalisation was the primary efficacy endpoint of the trial. A total of 34 (5.3%) of the 639 children in the palivizumab group met the primary endpoint of RSV hospitalisation compared to 63 (9.7%) of the 648 children in the placebo group (p=0.003). This represents a 45% relative reduction of RSV hospitalisations among children receiving palivizumab. Three (0.5%) and 9 (1.4%) of the children in the palivizumab and placebo group had "nosocomial RSV hospitalisation". One (0.2%) child in each group died in the ER from RSV bronchiolitis; these deaths were included as RSV hospitalisations. In each year of the study, the incidence of RSV hospitalisation was lower in the palivizumab group than in the placebo group with peaks in December, January and February.

Primary Analysis	**Palivizumab** (n=639)	**Placebo** (n=648)	**p-value**
RSV hospitalisation	34 (5.3%)	63 (9.7%)	0.003
No RSV Hospitalisation	605 (94.7%)	585 (90.3%)	

The number of non-completers was balanced between the treatment groups. Accounting for non-completers the result remained in favour of palivizumab. Results were robust in sensitivity analyses. When accounting for missing RSV antigen tests within the prespecified time frame in children who were hospitalised for acute cardiorespiratory illness that could have been caused by RSV (14 (2.2%) children in the palivizumab group and 9 (1.4%) in the placebo group) the result remained statistically significant in favour of palivizumab (p 0 0.004). The result was similar when accounting for children hospitalised with virological evidence for RSV but not meeting the protocol-defined criteria for RSV hospitalisation (p = 0.002).

A secondary analysis, accounting for the cardiac strata (cyanotic and 'other') by means of a Mantel-Haenszel test resulted in a p-value of 0.003. Although the number for RSV hospitalisation was in favour of palivizumab in both strata the effect was more pronounced in the 'other' stratum.

A logistic regression analysis was performed to assess the effect of predefined baseline variables (cardiac stratum, gender and age) on the primary study outcome. Beside the treatment group, only age was statistically significant, indicating a decreasing risk of RSV hospitalisation with increased age at study entry.

In general, the reduction of RSV hospitalisations was also consistent within subgroups of children defined by gender, age, weight, race, and presence of RSV neutralising antibody at entrance. The incidence of RSV hospitalisations in the palivizumab group was decreased relative to the placebo group, in the US 44%, in Canada 36% and Europe 57%.

Secondary efficacy endpoints were used to describe the RSV disease severity in hospitalised patients. For quantitative parameter the results of these endpoints were expressed as total days per 100 randomised children. The results are summarised below:

	Palivizumab N=639	**Placebo** N=648	**% Reduction**	**p-value**
Days of RSV Hospitalisation				0.003
Total Days/100 Children	57.4	129.0	56%	
RSV Hospital Days of Increased Supplemental Oxygen Therapy				0.014
Total Days/100 Children	27.9	101.5	73%	
ICU Admission				0.094
Yes	13 (2.0%)	24 (3.7%)	46 %	
Days in ICU Stay				
Total Days/100 Children	15.9	71.2	78%	
Mechanical Ventilation				0.282
Yes	8 (1.3%)	14 (2.2%)	41%	
Days of Mechanical Ventilation				0.224
Total Days/100 Children	6.5	54.7	88%	

All secondary efficacy endpoints revealed an advantage in favour of the palivizumab group. The number of hospitalisation days in the palivizumab group (57.4 days per 100 children vs. 129 days; p=0.003) was relatively reduced by 56%. A smaller percent of palivizumab than placebo patients (27.9 days per 100 children vs. 101.5 days; p=0.014; relative reduction 73%) had an increased need for supplemental oxygen therapy in the hospital. The palivizumab group also showed a similar trend towards fewer ICU admissions and mechanical ventilation as well as towards days in ICU stay and days of mechanical ventilation as compared to placebo.

Administration of more than 5 doses

The half-life of palivizumab is 17-20 days, which is comparable to human IgG antibody. To maintain a target trough level of 30 mcg/ml, it is essential that injections be given every 30 days to maintain adequate protective trough levels throughout the entire RSV season. From the original authorisation the number of doses utilised in both large randomised trials was based on the average length of the RSV season (November through March) observed in the northern hemisphere temperate countries that participated in these studies (5 doses).

The current dosing recommendation for palivizumab is, 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season. Subsequent doses should be administered monthly throughout the RSV season. In warmer countries, the RSV season is frequently longer than in

temperate countries; therefore, more than five monthly injections may be required to maintain adequate palivizumab trough levels to ensure protection over the entire RSV season.

Since the original authorisation, data has been collected regarding the safety of administration of more than 5 doses of palivizumab.

Clinical Efficacy:

The Abbott Study W00-350 was a phase II, open label, prospective trial designed to assess pK and safety issues in premature or BPD/CLD infants receiving up to 7 monthly i.m. injections of Palivizumab at doses of 15mg/kg. Eighteen children were enrolled and 17 completed treatment.

Palivizumab Assay Results

Study Visit*	Number of Subjects					Mean ± Standard Deviation†
	≥30 mcg/ml	<30 mcg/ml	<LOQ	NRP	Total	
Visit 1	0	0	15	0	15	0 ± 0
Visit 2	13	1	1	0	15	47.04 ± 18.44
Visit 5	18	0	0	0	18	127.89 ± 39.69
Visit 7	11	0	0	1	12	137.99 ± 47.91

N = 18

LOQ = limit of quantification, mcg/ml = mcg/ml of palivizumab, NRP = not reported

* Blood was drawn prior to study drug administration at each visit

† Values below the lower limit of quantification were excluded from analysis.

The study showed that serum palivizumab levels are similar after the 7th and 5th doses of palivizumab and were within the range of those observed in previous palivizumab studies. There was no indication of a fall in serum palivizumab levels with increasing number of doses and no evidence of drug accumulation. Serum levels were within the range previously correlated with protection.

Safety

Safety data demonstrate that palivizumab at a dose of 15 mg/kg IM is safe and well tolerated. In general, there were few differences in adverse event (AE) incidence between patients who had received palivizumab and those who had received placebo. Site of injection reactions occurred in 1.8% of placebo patients and 3.5% of palivizumab recipients. The most common IM reaction was erythema (1.2% placebo patients, 1.7% palivizumab) and this was transient and generally mild in severity. The incidence of diarrhoea related to study drug was 0.3% in the placebo group and 0.9% in the palivizumab group. Rashes occurred slightly more often in patients treated with palivizumab than placebo. Elevation of liver enzymes was measured more often in palivizumab treated patients than in the placebo group.

No medically important differences were observed in AEs by body system or when evaluated in subgroups of children by clinical category, gender, age, gestational age, country, race/ethnicity, or quartile serum palivizumab concentration. No significant difference in safety profile was observed

between children without active RSV infection and those hospitalised for RSV. Permanent discontinuation of palivizumab due to a drug-related AE was rare (0.2%). Deaths were balanced between the integrated placebo and palivizumab groups and were not drug-related. Although patients across the studies experienced a relatively large number of total AE and serious AE, these were in general matched between the palivizumab and placebo groups and are typical of prematurity and BPD.

Children less than two years of age and with haemodynamically significant congenital heart disease

In study MI-CP048 Results, the incidence of serious adverse events was lower in the palivizumab group compared with the placebo group. No fatalities were attributed to the study drug and generally there are no indications that the drug will exhibit safety problems in the CHD patient population that would not be reflected in the total population receiving palivizumab.

A total of 1236 patients (96%) reported 8687 adverse events with a similar distribution between the two treatment groups. Adverse events concerning the respiratory system were the most commonly reported (in 83.3% of the patients), followed by digestive (51.8%) and cardiovascular (46.7%) events. Adverse events mapping to the other body systems were balanced between treatment groups, whether as a whole or when evaluated by cardiac strata.

The overall distribution of adverse events by severity was similar between treatment groups, as well as within each stratum, for each of the body systems.

Adverse events with an incidence ≥ 1% and higher in the Palivizumab Group compared to Placebo

The incidence of adverse events by COSTART preferred term that were reported in ≥1% of palivizumab patients during the study was similar to the rates in the placebo group.

Fever occurred in 27.1% of palivizumab treated infants versus 23.9% of placebo treated infants. However, fever higher than 40.5º persisting >48 hours occurred only in 1 (0.2%) patient in the placebo group.

Infection was reported in 36 (5.6%) patients in the palivizumab group and 19 (2.9%) patients in the placebo group. Events occurred at low frequency and no adverse event was related to study drug. The incidence of bacterial, fungal, parasitic or viral infections were balanced between treatment groups. Viral infections and sepsis were reported in 41 (6.4%) and 14 (2.2%) patients, respectively in the palivizumab group and 48(7.4%) and 17 (2.6%) patients, respectively in the placebo group.

Upper Respiratory Tract Infection was reported in 303 (47.4%) patients in the palivizumab group and 299 (46.1%) in the placebo group. Related adverse events occurred rarely, related SAEs never. SAEs were balanced with 31 (4.9%) patients in the palivizumab group and 25 (3.9%) patients in the placebo group.

Arrhythmia was reported in 20 (3.1%) and 11 (1.7%) patients in the palivizumab and placebo groups, respectively. No adverse event was judged to be related to study drug

Adverse events coding to cyanosis were reported in 58 (9.1%) patients in the palivizumab group and 45 (6.9%) patients in the placebo group. Adverse events coding to preferred terms for cardiovascular conditions related to cyanosis were either balanced or favoured palivizumab. Adverse events coding to preferred terms for respiratory conditions related to cyanosis were balanced between treatment groups.

In summary, cyanosis and cyanotic events were balanced equally between palivizumab and placebo groups in CHD patients as a whole, and in the cyanotic stratum of patients in this study.

Because the target CHD patient population is extremely fragile, a post marketing safety surveillance program was considered necessary.

Administration of more than 5 doses

Palivizumab has been licensed in 50 countries worldwide. The product is used in countries with tropical climates where the RSV season may be prolonged. Since the current labelled dosing recommends administration of palivizumab in terms of season length, rather than specific months, palivizumab has been administered for more than 5 months in such areas. As a result, postmarketing data has been accumulated where infants have received more than 5 doses of palivizumab. These data are limited in that no one collection of data address all key components of a safety assessment previously indicated to be relevant to palivizumab: clinical adverse events, pharmacokinetics, and immunogenicity. The sources of these data are a postmarketing patient registry, the Abbott Pharmacovigilance safety database, and the results from the small clinical trial (W00-350).

From the clinical study W00-350, subjects were observed for adverse events related to palivizumab use. Only one subject tested positive for RSV during the study. None of the reported adverse events were considered related to palivizumab and no deaths were reported. The postmarketing data is presented in the *Post marketing Experience section.*

The MAH has provided evidence that the injection of up to 7 doses of palivizumab does not lead to more adverse events in the target patient population. However, the MAH has not provided convincing data to support that the product may be given at monthly interval for more than 7 months. The wording of the SPC clearly reflects this.

Immunogenicity

Because palivizumab is a monoclonal antibody with 5% murine antibody sequences the attention is focused on adverse events that could be immune-mediated. Although no significant formation of anti-palivizumab antibodies and no associated clinical adverse reactions have been shown in previous clinical trials, it remains unclear whether in this trial patients receiving palivizumab prophylaxis developed RSV neutralising antibodies

The potential sensitising properties of repeated injections with Palivizumab was assessed in the W00-350 study in Saudi Arabia. Only one subject out of eighteen had a transient, minimal elevation of anti-palivizumab antibody titre after the second dose and elevations were not observed in the other subjects.

Post-marketing experience:
With regard to the events reported during the post-marketing experience, the SPC has been updated to include a warning related to the fact that injections of palivizumab may be associated with the risk of allergic and anaphylactic reactions, as well as a warning on the necessity that medications for the treatment of severe hypersensitivity reactions should be available for immediate use following administration of palivizumab.
Furthermore, "*Apnoea"* has been included as a rare adverse drug reaction and "*Anaphylaxis, urticaria",* as a very rare adverse drug reaction in the SPC.

Because palivizumab is a monoclonal antibody comprised in small part of murine antibody sequences (5%), careful attention was given throughout the clinical program to AEs, which could be immune-mediated. This investigation revealed no evidence of a clinically significant immune response directed against palivizumab. During the first prophylactic course with palivizumab reactivity (i.e. human anti-human antibodies - HAHA) was low (approximately 1%), transient and of low titre. One of the 56 children who received palivizumab during a second RSV-season developed HAHA, which resolved despite continued use of palivizumab. Two children with pre-existing low-titred HAHA did not develop anti-palivizumab antibodies during the second winter on palivizumab. Thus, the observed HAHA appear not to be of clinical relevance.

Considering the enhancement of the severity of disease induced by the use of a formalin-inactivated RSV vaccine, specific efforts were made to assess this particular issue. Extensive preclinical

(see pharmacodynamics) and clinical data suggest that RSV antibodies, and in particular palivizumab, do not enhance the severity of RSV disease, but rather reduce the RSV pulmonary replication and reduce the incidence of hospitalisation in children.

In the randomised, placebo-controlled treatment study, MI-CP026, tracheal washes of children intubated for severe RSV disease were titred for RSV before treatment and daily thereafter. The next table shows the mean tracheal RSV titre for the placebo and palivizumab groups, both of which had mean titres of 4.8 log10 before treatment. At two days after treatment, the mean tracheal RSV titre had declined by 1.0 $\log_{10}$ in placebo recipients and by 2.5 $\log_{10}$ in palivizumab recipients (p=0.012).

RSV plaque assay titre ($\log_{10}$) in tracheal aspirate, MI-CP026

	Placebo N=18	Palivizumab N=16	p-value
Mean titre (SE) at study entry (day 0)	4.8 (0.3)	4.8 (0.3)	
Decrease in titre on			
Day 1	0.6 (0.2)	1.7 (0.3)	0.004
Day 2	1.0 (0.4)	2.5 (0.3)	0.012

The clinical studies including the pivotal and phase I/II (MI-CP009 and MI-CP013) indicate that Synagis does not enhance RSV disease severity. The results from MI-CP009 and MI-CP013 as presented in the next table show no significant difference in the duration of hospitalisation, days of hospitalisation requiring oxygen therapy or days of mechanical ventilation between placebo and palivizumab groups.

Number of patients	Placebo N=36	Palivizumab N=37
Days of RSV hospitalisation		
Total days	218.0	162.6
Mean days	6.05 (1.04)	4.39 (0.68)
Days/100 patients	589.1	439.5
Days of mechanical ventilation		
Total days	39.6	33.0
Mean days	7.91 (2.62)	4.71 (1.01)
Days/100 patients	106.9	89.1
Days of increased supplemental O_2		
Total days	42.0	37.0
Mean days	3.23 (1.22)	2.47 (0.41)
Days/100 patients	113.5	100.0

No formal drug interaction studies have been performed with palivizumab. However, given the specificity of the monoclonal antibody to RSV it would not be expected to interfere with live viral vaccines, as is the case with immune preparations. In addition, given the normal metabolic pathway of immunoglobulins, no interaction would be expected between palivizumab and medications, which are cleared by the liver or kidney. In the pivotal trial, no specific adverse events attributable to the interaction of palivizumab and corticosteroids, bronchodilators, routine childhood immunisations or influenza vaccine were evident.

Palivizumab is estimated to be given to 55,000 children in US during the 1998-1999 respiratory disease season. An analysis of available postmarketing data in US lead to the conclusion that these data do not change the safety profile of palivizumab. These data come either from spontaneous reports or through the company's RSV education and compliance helpline (REACH programme) which follows 7,001 children.

Post marketing surveillance

Post marketing Clinical Surveillance Program (REACH)

The population of infants followed in this program represented 13% of the estimated total population in infants who received palivizumab in the United States during the two years it was conducted. The total number of infants enrolled in the REACH program reached almost 20,000 infants.

Adverse events occurred in 1% of infants receiving 6 or more doses. It is claimed that all of the adverse events occurring after administration of a 6th or greater dose occurred with the 6th dose and not with subsequent doses (up to 9 doses). The estimated frequency of adverse events with each dose was similar irrespective of the dose number. In addition, the nature of the adverse events that were reported in 15 children was similar to those previously observed in the IMpact trial, and subsequently observed in MI-CP048.

Abbott Post marketing Safety Surveillance

The Abbott Postmarketing Safety database was searched for all palivizumab serious adverse event reports received from the international birth date (19 June 1998) to 19 June 2002, encompassing four complete seasons of palivizumab use. A convention to identify serious cases occurring in infants who received 6 or more doses were developed. In contrast to the REACH database, this approach does not allow an estimation of frequency, as there was no way to ascertain the total number of children who had received 6 or more doses of palivizumab. The character of the serious adverse events was compared between the groups in infants who received 5 or fewer doses of palivizumab in a single season, and those who received 6 or more doses.

A total of 1291 serious adverse events were identified, 73 of which could be identified as occurring in patients receiving 6 or more doses of palivizumab in a single RSV season. The adverse events described in patients receiving 6 or more doses of palivizumab were similar in character to the adverse events described in patients who received fewer than 6 doses or an unspecified number of doses. Fifty-one of these patients experienced an adverse event after one of the first 5 doses, 19 patients after receiving a sixth or greater dose, and three patients experienced adverse events both after one of the first five doses and after six or greater doses. The events in these three patients were disparate and were related to a previously existing underlying condition in two (reactive airway disease and reflux). The small number of any specific event occurring after 6 or more doses prevents a conclusion regarding relative frequency, but the pattern of events does not indicate a pattern of hypersensitivity or other adverse event when 6 or more doses of palivizumab were administered.

5. Overall conclusions and benefit/risk assessment

Safety data demonstrate that palivizumab at a dose of 15 mg/kg IM is safe and well tolerated. The efficacy of palivizumab was assessed with regard to the facts, that RSV is the most common cause of LRI in infants, especially in those of premature gestation and BPD and that serious RSV disease is the primary cause of rehospitalisation of these infants. The reduction of the RSV hospitalisation rate by 55% and the reductions in all secondary endpoints except those with low frequency provide medically significant evidence of efficacy. Thus, over half the children were spared hospitalisation, the complications of a severe disease course and the stress of subsequent treatment regime.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of Synagis was favourable 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.

5 year Renewal:

Based on the CHMP review of the available information, the CHMP considered that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of Synagis continues to be favourable.

The Committee for Human Medicinal Products recommended therefore the renewal of the Marketing Authorisation for Synagis, provided that the MAH agrees to submit annuals PSURs and in the PSURs closely focus on the safety data with respect to *a*) risk of enhanced RSV infection in the 2nd season, *b)* the new target population CHD-children and *c)*children receiving more than 5 doses annually.