CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103770/S-5033

Trade Name: **SYNAGIS**

Generic Name: **Palivizumab**

Sponsor: **MedImmune, Incorporated**

Approval Date: 09/15/2003

Indications: Synagis® is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant CHD.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

SEP 15 2003

Our STN: BL 103770/5033

Peter Patriarca, M.D.
Vice President, Regulatory Affairs
MedImmune, Incorporated
35 West Watkins Mill Road
Gaithersburg, MD 20878

Dear Dr. Patriarca:

Your request to supplement your biologics license application for Palivizumab to expand the indication to include children with hemodynamically significant congenital heart disease has been approved.

This fulfills your commitment to conduct a safety study in pediatric congenital heart disease patients, as stated in commitment number 2 of the June 19, 1998, approval letter.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

FOR P.K.

Patricia Keegan, M.D.
Acting Director
Division of Clinical Trials Design and Analysis
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
LETTER: Fulfillment of PMC (FPC)
Summary Text: Clinical Supplmt. – Labeling Only
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:
- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:
- **Verify short summary – Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs – add "PMCs – Approved With" special characteristic code.)**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: HFM-555/K. Webber
HFM-561/S. Kozlowski
HFM-570/P. Keegan
HFM-570/M. Walton
HFM-585/DARP BLA file
HFM-500/K. Weiss
HFM-4/QAS
HFM-110/RIMS
HFM-602/C. Broadnax, APLB, (with final draft PI)
HFD-322/E. Rivera-Martinez, IPCB,
HFM-40/OCTMA, (with final draft PI)
HFM-670/DMPQ Blue file
HFM-570/P. Lincoln-Smith
HFM-588/D. Slavin
HFM-582/L. Marzella
HFM-582/L. Forsyth
HFM-579/H. Zhao
HFM-219/B. Zhen
HFM-650/J. L. Johnson

History: Slavin:9-11-03

File Name: S:\Slavin\Letters\BLA\Palivizumab\103770.5033\103770.5033AP

Office	Name/Signature	Date
OTRR		9-15-03

OTCA/DARP	Karen D Jones	9/16/03
DARP	Dep for Jones	9-15-03
DCTDA	Linda M. Forsyth	9-15-03
DCTDA	M Wade FOR PK.	9/15/03
DARP	Kelley Townsend	9/17/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

LABELING

SYNAGIS® (PALIVIZUMAB)
for Intramuscular Administration

DESCRIPTION: Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis® is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® is to be administered by intramuscular injection (IM) only. Upon reconstitution, Synagis® contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL solution. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis® exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (5). Synagis® serum concentrations of ≥ 40 µg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The in vivo neutralizing activity of the active ingredient in Synagis® was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, Synagis significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients less than 24 months of age without congenital heart disease, the mean half-life of Synagis® was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ±SD 30 day trough serum drug concentrations of 37+ 21 µg/mL after the first injection, 57 ± 41 µg/mL after the second injection, 68 ± 51 µg/mL after the third injection and 72 ± 50 µg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis dose were similar in children with congenital heart disease and in non-cardiac patients. In pediatric patients given Synagis® for a second season, the mean ±SD serum concentrations following the first and fourth injections were 61 ±17 µg/mL and 86 ±31µg/mL, respectively.

In 139 pediatric patients ≤ 24 months of age with hemodynamically significant congenital heart disease (CHD) who received Synagis® and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis® concentration was 98± 52 µg/mL before bypass and declined to 41± 33 µg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis® systemic exposure. However, no effects of gender, age, body weight or race on Synagis® serum trough concentrations were observed in a clinical study with 639 pediatric patients with congenital heart disease (≤24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis®

CLINICAL STUDIES: The safety and efficacy of Synagis® (palivizumab) were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1,502 patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg Synagis® or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

Table 1: **Incidence of RSV Hospitalization by Treatment Group**

Trial		Placebo	Synagis	Difference between groups	Relative Reduction	p-Value
Trial 1 Impact-RSV	N	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55	<0.001
Trial 2 CHD	n	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis®), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%]) Synagis®). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis® and cyanotic children (27/343 [7.9%]) placebo versus 19/339 [5.6%] Synagis®.

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis compared to those who received placebo.

INDICATIONS AND USAGE: Synagis® is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant CHD. (See *CLINICAL STUDIES*)

CONTRAINDICATIONS: Synagis® should not be used in pediatric patients with a history of a severe prior reaction to Synagis® or other components of this product.

WARNINGS: Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to Synagis® (see *ADVERSE REACTIONS, POSTMARKETING EXPERIENCE)*. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to Synagis®. If a severe hypersensitivity reaction occurs, therapy with Synagis® should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis®. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis® is for intramuscular use only. As with any intramuscular injection, Synagis® should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Injections should be given within 6 hours after reconstitution. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis® groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not performed.

Pregnancy: Pregnancy Category C: Synagis® is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS:

The most serious adverse reactions occurring with Synagis® treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in Synagis®-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis® group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis® exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease.

Table 2 - Adverse events occurring at a rate of 1% or greater more frequently in patients† receiving Synagis®

Event	Synagis® (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)

†Cyanosis (Synagis® [9.1%]/ placebo [6.9%]) and arrythmia (Synagis® [3.1%]/placebo [1.7%]) were reported during Trial 2 in congenital heart disease patients.

Immunogenicity

In the Trial 1, the incidence of anti-Synagis® antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® group. In pediatric patients receiving Synagis® for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® with the incidence of antibodies to other products may be misleading.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of Synagis®. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure *(*See *WARNINGS)*. None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis® are similar in character and frequency to those after the initial five doses.

OVERDOSAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis® is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis® serum levels are decreased after cardio-pulmonary bypass (*See CLINICAL PHARMACOLOGY*). Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis® as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Synagis® should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis®. Injection volumes over 1 mL should be given as a divided dose.

Preparation for Administration:

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- SLOWLY add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® should stand at room temperature for a minimum of 20 minutes until the solution clarifies.

- Reconstituted Synagis® (palivizumab) should be inspected visually for particulate matter or discoloration prior to administration. The reconstituted solution should appear clear or slightly opalescent. Do not use if there is particulate matter or if the solution is discolored

- Reconstituted Synagis® does not contain a preservative and should be administered within 6 hours of reconstitution. Synagis® is supplied in single-use vials. DO NOT re-enter the vial. Discard any unused portion.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED: Synagis® is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1
Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4111-1
Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® should be stored between 2 and 8°C (35.6° and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

REFERENCES:

1. Press E, and Hogg N. The amino acid sequences of the Fd Fragments of Two Human gamma-1 heavy chains. Biochem. J. 1970;117:641-660.

2. Takahashi N, Noma T, and Honjo T. Rearranged immunoglobulin heavy chain variable region (V_H) pseudogene that deletes the second complementarity-determining region. Proc. Nat. Acad. Sci. USA 1984;81:5194-5198.

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4. Beeler JA, and Van Wyke Coelingh K. Neutralization epitopes of the F Protein of Respiratory Syncytial Virus: Effect of mutation upon fusion function. J. Virology 1989;63:2941-2950.

5. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J. Infect. Dis. 1997; 176:1215-1224.

6. Malley R, DeVincenzo J, Ramilo O, et al. Reduction of Respiratory Syncytial Virus (RSV) in Tracheal Aspirates in Intubated Infants by Use of Humanized Monoclonal Antibody to RSV F Protein. J. Infect. Dis. 1998;178:1555-1561.

7. The IMpact RSV Study Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. Pediatrics 1998;102:531-537.

Manufactured by:

MedImmune, Inc.
Gaithersburg, MD 20878
U.S. Gov't. License No. 1252
(1-877-633-4411)

Co-Marketed by:

ROSS Ross Products Division
Abbott Laboratories, Inc.
Columbus, OH 43215-1724

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852
September 15, 2003

From: Linda M. Forsyth, M.D., Clinical Reviewer, Immunology and Infectious Diseases

Through: Lou Marzella, M. D., Ph.D. Team Leader, Immunology and Infectious Diseases

Marc Walton, M. D., Acting Director, Division of Therapeutic Biologic Internal Medicine Products, Office of Drug Evaluation VI, CDER, FDA

To: SUPPLEMENTAL BIOLOGICS LICENSE APPLICATION
FDA CLINICAL REVIEW
#STN 103770/5033
PALIVIZUMAB (SYNAGIS)
MEDIMMUNE, Inc.
Efficacy Supplement for Infants with Congenital Heart Disease

Clinical Reviewer: Linda M. Forsyth, M.D.
Clinical Team Leader: Lou Marzella, M.D., Ph.D.
Biostatistics Reviewer: Bo Zhen, Ph.D.

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PALIVIZUMAB (SYNAGIS) #STN 103770/5033

INTRODUCTION

On November 14, 2002 the sponsor, MedImmune, Inc., submitted to STN 103770/5033 a labeling supplement pertaining to the safety and efficacy of palivizumab (respiratory syncytial virus F-protein-specific humanized monoclonal antibody) in infants with congenital heart disease.

Palivizumab was licensed by FDA in 1998 for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease, and safety and efficacy was established in infants with bronchopulmonary dysplasia and prematurity. Children with congential heart disease (CHD) are at particular risk for severe RSV disease. The supplemental (s)BLA is the final step of a post-marketing commitment made by the sponsor to study the product in this patient population.

The submission contains a complete report of study MI-CP048 entitled: "A Study of the Safety, Tolerance, and Efficacy of Palivizumab (MEDI-493, Synagis®) for Prophylaxis of Respiratory Syncytial Virus in Children with Congenital Heart Disease".

The submission also contains a revised package insert (PI) that describes the efficacy and safety findings of study MI-CP048 in the "Clinical Study" section of the PI and proposes the addition of the following additional indication: Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children with hemodynamically significant CHD.

Clinical Manifestations of RSV

RSV, an enveloped RNA virus of the paramyxovirus family, is a common human respiratory pathogen and major cause of respiratory tract illness in children. RSV infection is generally acquired via particle inoculation of nasal or lachrymal mucosa from large droplets (or contact with contaminated secretions). Most RSV infections manifest as respiratory tract disease and asymptomatic infection is uncommon. Severe RSV disease usually manifests as bronchiolitis or pneumonia and is primarily a disease of infants and immunosuppressed individuals. Infants at the greatest risk for severe manifestations of RSV infection include those with history of prematurity, immunodeficiency, congential heart disease or chronic lung disease. 50-70% of all infants experience RSV infection in the first year of life and almost all are infected by two years of age. RSV causes more than 90,000 hospitalizations and 4,500 deaths in the United States annually. It is estimated several hundred thousand infants are at risk for RSV although severe respiratory disease will only develop in less than 1% of these infants. Primary infection with RSV is not protective against subsequent infections. Clinical manifestations vary by age. Infection in young children may manifest as lower respiratory tract diseases such as pneumonia, bronchiolitis, tracheobronchitis or upper respiratory tract disease and otitis media. Infants usually manifest pneumonia or bronchiolitis in response to RSV infection. Usually 2-4 days after exposure to RSV, bronchiolitis and pneumonia develops in infants and manifests as fever and cough. Tachypnea and labored respirations follow and hypoxemia is common among those infants requiring hospitalization. Infants under six months are at high risk for pneumonia and bronchiolitis. Infections in older children and adults usually manifest with cough and coryza.

STUDY PROTOCOL

Study Title and Number

" A Study of the Safety, Tolerance, and Efficacy of Palivizumab (MEDI-493, Synagis®) for Prophylaxis of Respiratory Syncytial Virus in Children with Congenital Heart Disease" MI-CP048.

Study Design

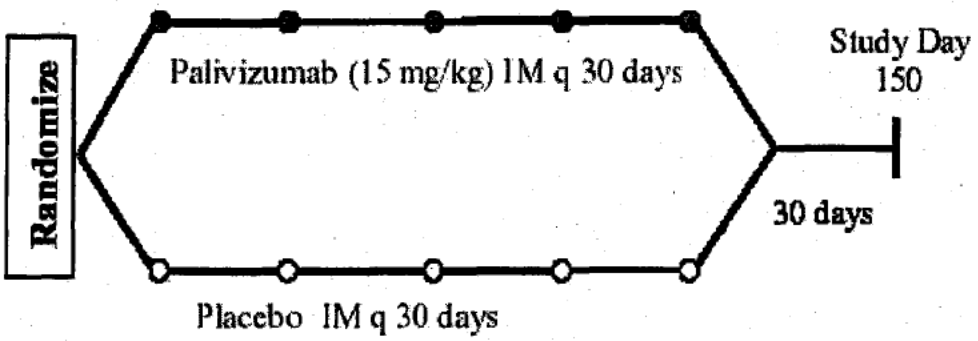
Phase 4 (Post marketing commitment), randomized, double-blind, placebo-controlled, multi-center, multinational (US, Europe, and Canada) study of 5 monthly injections of 15 mg/kg palivizumab during the Respiratory Syncytial Virus (RSV) season in approximately 1280 children with congenital heart disease. Children were randomized to one of two arms: Arm I-Palivizumab, 15 mg/kg (0.15 mL/kg) intramuscular (IM) Study Days 0, 30, 60, 90, 120 or Arm II-Placebo (0.15 mL/kg) IM Study Days 0, 30, 60, 90, 120 and were followed for 30 days after the last treatment. Randomization (1:1) was blocked by site and stratified according to whether the patient had anatomical cyanotic CHD.

Stratification: Cyanotic vs. Acyanotic lesions
Prior to randomization, each patient was categorized as to whether the heart defect was cyanotic or non-cyanotic. This was to help ensure balance between the treatment arms for lesions which were likely to lead to more serious adverse experiences during the study period. The classification was based on the anatomy of the defect, not on the basis of the oxygen saturation at study entry. The stratification was determined by whether or not the primary lesion was included in the list below of the most common cyanotic lesions. If so, the patient was randomized in stratum 1, the cyanotic stratum. Otherwise, the patient was randomized with the non-cyanotic stratum 2, even though the actual lesion would be medically classified as cyanotic.

Stratum 1 (Cyanotic)
- Pulmonary atresia with VSD
- Pulmonary atresia with intact septum
- Tetralogy of Fallot
- Single ventricle including hypoplastic left or right heart
- Tricuspid atresia
- Double outlet right ventricle with transposed great arteries
- Ebstein's anomaly
- D-transposition of the great arteries ± ventricular septal defect ± pulmonary stenosis

Stratum 2 (non-Cyanotic)
Any lesion not listed above

Diagram of study design



Inclusion Criteria

Patients who met all of the following criteria were eligible for entry into the study:

- Age 24 months or younger at the time of randomization
- Documented hemodynamically significant congenital heart disease (*Note: Children with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus were not eligible)*
- Unoperated or partially corrected congenital heart disease

Exclusion Criteria

- Unstable cardiac or respiratory status, including cardiac defects so severe that survival was not expected or for which cardiac transplantation was planned or anticipated
- Hospitalization, unless discharge was anticipated within 21 days
- Anticipated cardiac surgery within 2 weeks of randomization
- Requirement for mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support
- Associated non-cardiac anomalies or end organ dysfunction resulting in anticipated survival of <6 months or unstable abnormalities of end organ function
- Known to be HIV positive
- Acute RSV or other acute infection or illness *(A negative RSV antigen test at study entry was required for children with respiratory symptoms)*
- Previous administration of palivizumab or other monoclonal antibodies
- Use of intravenous immune globulin (IGIV), including RSV-IGIV (RespiGam®), within 3 months prior to randomization or anticipated use of IGIV, RSV-IGIV or open-label palivizumab during the study period

Primary Efficacy Outcome

The primary efficacy endpoint was incidence of RSV hospitalization. This endpoint was defined as either a cardiac/respiratory hospitalization in which an RSV antigen test was positive within 48 hours of hospital admission, or a "nosocomial RSV hospitalization" in which a hospitalized patient experienced an objective measure of worsening respiratory status with a positive antigen test. In addition, children who died outside the hospital with disease that could be demonstrated to be associated with RSV were considered an endpoint event. Patients who did not complete the study prior to reaching an endpoint or did not have an RSV antigen test performed were counted as not reaching an RSV endpoint.

Secondary Efficacy Outcomes

Secondary efficacy endpoints were: total days of RSV hospitalization, total RSV hospital days with increased oxygen requirement, incidence and total days of RSV-associated intensive care, and incidence and total days of RSV-associated mechanical ventilation. Total days were summarized per 100 children randomized.

Reviewer's comment: Total days of RSV hospitalization and total days with oxygen requirement is a poor choice for endpoint. It might be statistically significant but it is difficult to interpret.

Clinical and Laboratory Assessments

A table of the study procedures including safety and efficacy assessment is displayed under Table 34 in the Appendix.

The protocol also contained detailed procedures for evaluation of patients and collection of data for the purpose of assessing primary and secondary outcomes. These procedures are summarized below.

Hospitalizations
All hospitalizations were identified from the time of randomization through Study Day 150. For children randomized while in the hospital, that hospitalization was not defined as a study hospitalization unless a serious adverse event was reported after randomization (i.e., hospitalization was prolonged) or if the hospitalization became a "nosocomial RSV hospitalization." In addition to inpatient hospitalization, the following medical events were reported as hospitalizations: any outpatient cardiac surgical procedure; interventional cardiac catheterizations (including outpatient); outpatient procedures for which the patient required overnight medical observation; medical management in the emergency room (ER) or holding area for >=24 hours.

Cardiac/Respiratory Hospitalizations
A Cardiac/Respiratory hospitalization was one occurring after randomization for which the primary reason for admission was evaluation or treatment of a cardiac/respiratory condition. Cardiac/respiratory hospitalizations were further divided into 1) those in which

the admission was due to an acute cardiac or respiratory illness or 2) those for a planned surgical procedure or diagnostic testing not associated with an acute illness. Information about the reason for hospitalization was available from a) the admission diagnosis on the hospital admission case report forms (CRF) and b) the reported serious adverse event (SAE) term from that admission. The admission diagnosis on the hospital admission CRF was designed to reflect the initial impression at the immediate time of admission and was obtained from the admission hospital record. The SAE term for the hospitalization was designed to distinguish hospitalization for intercurrent cardiac/respiratory illness (where the reported term was the medical event that precipitated the admission) from hospitalization for diagnosis or planned intervention for the underlying disease (where the reported term was the specific heart malformation). The SAE term was used to classify Cardiac/Respiratory hospitalizations into those with an acute cardiac or respiratory illness and those without acute illness as described above.

RSV Hospitalizations and Antigen Testing
RSV antigen testing was to be performed on respiratory secretions (nasal swab or nasal wash) of all children with cardiac/respiratory hospitalizations associated with an acute illness within 48 hours of admission. Children with respiratory illnesses who had an initial negative RSV antigen test may have had the test repeated (within 24 hours) if the physician continued to suspect RSV as a causative agent. In addition, RSV antigen testing was to be performed in children who were hospitalized for any reason and subsequently experienced a cardiac/respiratory deterioration.

Hospitalized children also had the following data collected: the date and time of admission; initial reason for admission; the presence/absence of specified respiratory signs/symptoms; and cardiac status and oxygen requirement on admission. During hospitalization information was collected regarding requirement for increased supplemental oxygen, intensive care unit (ICU) requirement and duration, and mechanical ventilation requirement and duration.

A primary RSV hospitalization was defined as a cardiac/respiratory hospitalization, for reasons other than planned surgery or diagnostic testing without acute illness, in which the RSV antigen test was positive within 48 hours before or after admission. For analytic purposes, any cardiac/respiratory hospitalization in which the admission was due to an acute cardiac/respiratory illness (that was reported as a SAE) that had a positive antigen within 48 hours of admission was considered a primary RSV hospitalization. Deaths occurring outside the hospital that could be demonstrated to be associated with RSV (by autopsy or clinical history and virologic evidence) were also considered as primary RSV hospitalization endpoints. A "nosocomial RSV hospitalization" was defined as one in which hospitalized patients experienced an objective measure of worsening respiratory status (defined as a cardiac/respiratory SAE with acute illness) and the RSV antigen was positive. Cardiac/respiratory deterioration was defined by the occurrence of a cardiac/respiratory SAE term indicating the onset of an acute cardiac/respiratory illness.

Cardiac Procedures
If a cardiac surgical procedure (including interventional catheterization) was performed, the procedure was to be identified and classified according to whether it was planned, earlier than planned but not unexpected based on the underlying defect, or urgent.

Reviewer's comment: The procedures summarized above were essential for systematic classification of hospitalization and cardiac procedures events and for RSV antigen testing. The procedures were designed to ensure capture of data needed to adjudicate the primary endpoint study.

The procedures for collecting and evaluating data needed for assessment of secondary endpoints and

Total Days of RSV Hospitalization were calculated from the date and time of RSV hospitalization to the date and time when the patient was discharged from the hospital, unless the hospitalization was prolonged for incidental reasons (e.g., elective pre-planned surgery or non-medical reasons such as social/custody reasons). The physician was to note such reason for prolonging the hospitalization and state the date and time the child would have been discharged for the RSV hospitalization. The onset of "nosocomial RSV hospitalization" was determined as the time of onset of a cardiac/respiratory SAE with an acute illness associated with a positive RSV antigen test.

Total RSV Hospital Days With Increased Oxygen Requirement was evaluated daily throughout each RSV hospital stay. The total RSV hospital days with increased oxygen requirement for those children receiving chronic oxygen was determined by the days with oxygen requirement increased above the most recently determined baseline.

Incidence and Total Days of RSV-Associated Intensive Care For each patient hospitalized with RSV, information was collected regarding the time and date of ICU admission and the time and date of ICU discharge. Information was collected regarding the medical indication for ICU care.

Incidence and Total Days of RSV-Associated Mechanical Ventilation For each patient hospitalized with RSV, the time and date of the beginning and end of mechanical ventilation were collected. The medical indication for mechanical ventilation was also recorded.

Effect of Cardiac Bypass on Serum Palivizumab Concentrations For patients who underwent cardiac bypass, serum palivizumab concentrations were to be determined before and the day after bypass.

Trough Serum Palivizumab Concentrations Mean trough serum palivizumab concentrations before the second injection and the fifth injection were summarized.

Statistical Analyses

Sample Size

This study was designed to test the hypothesis that palivizumab reduces the RSV hospitalization rate in children with CHD when compared to placebo. Assuming an RSV hospitalization rate of 12% in the placebo group compared to 7.2% in the treatment group, approximately 1280 children were to be randomized (1:1) to provide 80% power of showing a 40% reduction in the incidence of RSV hospitalizations using a 2-sided alpha of 0.05.

Data Analyses

The primary endpoint was the incidence of RSV hospitalization. The primary endpoint was compared between treatment groups using Fisher's exact test. Children with more than one RSV hospitalization were counted only once. A secondary analysis of the primary endpoint was performed using the Cochran-Mantel-Haenszel test to assess the treatment effect across cardiac strata. Intent-to-treat analysis ("as randomized") was used.

A secondary analysis of the primary endpoint was performed. All patients were classified into one of the following 3 categories: 1) had an RSV hospitalization, 2) had no RSV hospitalization through 150 days of follow-up, 3) had no RSV hospitalization but terminated the study before 150 days of follow-up. This third category included all reasons for premature study discontinuation. During this analysis deaths outside the hospital due to RSV (as determined by autopsy or by adequate clinical information assessed at an endpoint review prior to breaking the blind) was included as RSV hospitalization endpoints. A Kolmogorov-Smimoff test was used to compare the distributions between the two treatment groups. Interpretation of this secondary analysis included a review of the medical significance and causality of deaths and dropouts to evaluate reasons for any differences between groups in premature discontinuation.

A Kaplan-Meier analysis assessing time to first RSV hospitalization was used as a confirmatory test accounting for incomplete follow-up. Patients who did not have a RSV hospitalization during the study (i.e. complete study, withdrawal, or death prior to having a RSV hospitalization) were considered censored events. For these patients time was defined in days from the date of randomization to date of last follow-up. For patients experiencing a RSV hospitalization, time was defined from randomization to date of first RSV hospitalization. Estimates at Study Day 150 were determined and compared.

Logistic regression was also used to evaluate the influence of baseline covariates on RSV hospitalization. Baseline variables with potential prognostic value including age at study entry, gender and cyanosis status were included as covariates.

Baseline variables were compared between groups using Fisher's Exact test or Wilcoxon Rank Sum test where appropriate. The major safety variable was the incidence of treatment-emergent adverse events and serious adverse events compared between groups

using Fisher's Exact test. These were described by body system, severity and relationship to study group (as assessed by the blinded investigator).

Secondary variables including frequency of RSV ICU admission, RSV-related mechanical ventilation, and frequency of cardiac-related surgery (urgent, planned, sooner than planned, expected) would be analyzed using Fisher's exact test. The number of RSV hospital ICU days, days of RSV-related mechanical ventilation and RSV hospital days with increased oxygen requirement was compared between groups using Wilcoxon Rank Sum test and summarized per 100 randomized children.

Interim Efficacy Analysis

An independent Data Safety Monitoring Board (DSMB) monitored the study. During the trial when about 50% of the accrual had occurred, an interim analysis of efficacy was performed for assessment of rejection of the null hypothesis. The Lan-Demets procedure based on calendar time using O'Brien-Fleming-like boundaries was used. The following listing shows the p-values used to declare the treatments significantly different from each other and the changes that would occur if the timing of the interim look varied from the midpoint of the trial.

Analysis	Calendar time	O'Brien-Fleming, p-value
1	0.5	0.0031
2	1.0	0.0487
1	0.6	0.0076
2	1.0	0.0476
1	0.7	0.0148
2	1.0	0.0456

Any decision to terminate the trial early was to be based both on clinical and statistical considerations. Other parameters in addition to the primary endpoint which could have impacted the decision to continue or stop the trial included internal consistency of the data (e.g. secondary endpoints, subgroups) recruitment status, baseline comparability, compliance and adverse events. If appropriate, based on these other considerations, the DSMB could recommend continuation even if the boundary at the interim look was crossed. The DSMB consisted of a biostatistician, a pediatric infectious disease specialist, and a pediatric cardiologist. The members were not otherwise involved in the conduct of the trial and no DSMB members were employees of MedImmune. Annual reviews of safety were conducted by the DSMB.

Reviewer's comment: The protocol for the CHD study is similar in many respects to the protocol for the IMPACT study. The sponsor's proposed Clinical Study section of the label describes both protocols at length. Recommend that the description of the clinical trials be combined.

RESULTS

Patient Disposition, Baseline Demographics

A total of 1287 children were randomized at 76 sites in seven countries (US, Canada, France, Germany, Poland, Sweden, and the UK). The first patient was randomized on November 2, 1998 and the last study visit was completed on May 3, 2002. Of the 1287 children, 639 (49.7%) were randomized to the palivizumab group and 648 (50.3%) to the placebo group.

Overall, 96% of children in the palivizumab group and 96% in the placebo group completed the study (were followed for 150 days after randomization or reached the primary endpoint of RSV hospitalization). A high proportion of children (93% palivizumab and 92% placebo) received all 5 monthly doses of study drug.

Table 1 Disposition of Patients

Status	Palivizumab		Placebo	
Randomized	**639**		**648**	
Completed [1]	611	(96%)	619	(96%)
Not Completed	28	(4%)	29	(4%)
Fatalities [2]	19	(3%)	22	(3%)
Lost to Follow-up [3]	4	(1%)	3	(1%)
Withdrew Consent	5	(1%)	4	(1%)

[1] Defined as a child who reached a primary endpoint or was followed for 150 days after randomization.
[2] Fatalities exclude 7 patients (2 palivizumab, 5 placebo) who met the primary endpoint of RSV hospitalization.
[3] Unable to be contacted for endpoint assessment up to 150 days after randomization.

Reviewer's comment: There was a high rate of completion. Mortality rates were similar between treatment groups.

Table 2 Baseline Demographics

	Palivizumab (n=639)	Placebo (n=648)
Sex		
Male	349 (55%)	344 (53%)
Female	290 (45%)	304 (47%)
Race/Ethnicity		
Caucasian	453 (71%)	459 (71%)
Black	52 (8%)	61 (9%)
Hispanic	77 (12%)	66 (10%)
Asian	15 (2%)	21 (3%)
Other	42 (7%)	41 (6%)
Age at Study Entry (months)		
N	639	648
Mean (SE)	6.8 (0.2)	6.5 (0.2)
Median	5.1	5.0
Range	(0.1-24)	(0-24)
Weight at Study Entry (kg)		
N	638	646
Mean (SE)	6.1 (0.1)	6.0 (0.1)
Median	5.5	5.6
Range	(2-14)	(2-13)
Gestational Age (weeks)		
N	638	647
Mean (SE)	38.5 (0.1)	38.5 (0.1)
Median	39.0	39.0
Range	(28-43)	(26-42)
Multiple Birth		
Yes	27 (4%)	23 (4%)
No	612 (96%)	625 (97%)
Birth Weight		
N	637	646
Mean (SE)	3071.2 (25.8)	3086.2 (25.2)
Median	3125	3120
Range	(855-5160)	(638-4950)

Reviewer's comment: The study arms are balanced with respect to gender, age and ethnicity.

RSV Risk Factors and Cardiac Status at Baseline

Risk factors for RSV infection, presence and type of cardiac lesions and cardiac status were captured at the time of entry into the study and are summarized in the tables that follow.

Table 3 RSV Risk Factors at Study Entry

	Palivizumab (n=639)	Placebo (n=648)
Total N People in Household		
Mean (SE)	4.4 (0.1)	4.4 (0.1)
Median	4	4
Range	(2-12)	(2-12)
Patient in Daycare		
Yes	76 (12%)	69 (11%)
No	563 (88%)	579 (89%)
N Other Children in Daycare		
0	539 (84%)	532 (82%)
1	72 (11%)	94 (15%)
2	21 (3%)	12 (2%)
3	5 (1%)	8 (1%)
4	1(0%)	1(0%)
5	1 (0%)	0 (0%)
N Smokers in Household		
0	428 (67%)	424 (66%)
1	146 (23%)	130 (20%)
2	51 (8%)	79 (12%)
3	9 (1%)	10 (2%)
4	4 (1%)	3 (1%)
5	1 (0%)	0 (0%)
6	0 (0%)	1 (0%)
Atopy in Immediate Family		
Asthma		
Yes	172 (27%)	191 (30%)
No	450 (70%)	452 (70%)
Unknown	17 (3%)	5 (1%)
Hay fever		
Yes	174 (27%)	167 (26%)
No	448 (70%)	474 (73%)
Unknown	17 (3%)	7 (1%)
Eczema		
Yes	116 (18%)	120 (19%)
No	504 (79%)	522 (81%)
Unknown	19 (3%)	6 (1%)
Serum RSV Neutralization Ab Titer		
<1:200	372 (58%)	394 (61%)
>=1:200	170 (27%)	173 (27%)
Not Done	97 (15%)	81 (13%)

Table 4 IVRS [1] Stratification of Children by Cardiac Lesion

	Palivizumab (n=639)		Placebo (n=648)	
Stratification Classification				
Cyanotic	**339**	**(53%)**	**343**	**(53%)**
Pulmonary Atresia with VSD	45	(7%)	26	(4%)
Pulmonary Atresia with Intact Septum	20	(3%)	14	(2%)
Tetralogy of Fallot	75	(12%)	72	(11%)
Single Ventricle Incl. Hypoplastic Left or Right Heart	133	(21%)	149	(23%)
Tricuspid Atresia	29	(5%)	33	(5%)
Double Outlet Right Ventricle with Transposed Great Arteries	17	(3%)	21	(3%)
Ebstein's Anomaly	7	(1%)	11	(2%)
D-TGA with/without VSD and with/without Pulmonary Stenosis	13	(2%)	17	(3%)
"Other"[2]	**300**	**(47%)**	**305**	**(47%)**
Double Outlet Right Ventricle	10	(2%)	9	(1%)
Atrio-Ventricular Septal Defect	46	(7%)	47	(7%)
Ventricular Septal Defect	106	(17%)	126	(19%)
Atrial Septal Defect	28	(4%)	27	(4%)
Post-Operative Open-Heart Surgery	34	(5%)	33	(5%)
Patent Ductus Arteriosus	1	(0%)	4	(1%)
Left Heart Obstruction	25	(4%)	26	(4%)
Other	50	(8%)	33	(5%)

[1] Interactive Voice Response System
[2] Subclassification based on lesion description in CRF.
VSD=Ventricular septal defect. d-TGA=Transposition of the great arteries.

Reviewer's comment: Treatment groups are balanced with respect to RSV risk factors and cardiac lesions.

Table 5 Baseline Cardiac Status

	Palivizumab (n=639)	Placebo (n=648)
Cardiac Surgery or Interventional Catheterization		
Yes	396 (62%)	391 (60%)
No	243 (38%)	257 (40%)
Hypercyanotic Episode		
Yes	73 (11%)	84 (13%)
No	566 (89%)	564 (87%)
On Cardiac Medications		
Yes	484 (76%)	491 (76%)
No	155 (24%)	157 (24%)
Pulmonary Blood Flow		
Decreased or Normal	402 (63%)	395 (61%)
Increased	237 (37%)	253 (39%)
Pulmonary Hypertension		
<1/3 systemic	487 (76%)	484 (75%)
1/3 to 2/3 systemic	108 (17%)	124 (19%)
>2/3 systemic	44 (7%)	40 (6%)
Level of Cardiac Failure		
None	238 (37%)	220 (34%)
Controlled	395 (62%)	418 (65%)
Uncontrolled	6 (1%)	10 (2%)

Reviewer's comment: Treatment groups are comparable with regard to history of cardiac surgery or interventional catheterization, hypercyanotic episodes, need for cardiac medications, pulmonary blood flow status, presence of pulmonary hypertension and level of cardiac failure.

Primary Endpoint

The primary endpoint of the trial was a comparison of the rates of RSV hospitalization. Each patient is counted for a RSV hospitalization only once in the analysis. Decision regarding the need for hospitalization was made by the patient's physician. Hospitalizations were classified into:

- Due to cardiac and/or respiratory reasons.
- Other hospitalizations.

Table 6 Primary Analysis: Summary of Incidence of RSV Hospitalization

	Palivizumab (n=639)		Placebo (n=648)		P-value [1]
RSV Hospitalization [2]	**34**	**(5.3%)**	**63**	**(9.7%)**	**0.003**
No RSV Hospitalization	605	(94.7%)	585	(90.3%)	

[1] P-value was obtained from Fisher's exact test.
[2] Children with more than one hospitalization were counted only once.

All randomized children, regardless of the number of injections of study drug received, were included in the primary and secondary efficacy analyses related to RSV hospitalization, and in the safety analyses.

Reviewer's comment: This result is similar to the primary endpoint analysis in the first study in children with bronchopulmonary dysplasia and premature birth with 48/1002 (4.8%) RSV hospitalizations for palivizumab and 53/500 (10.6%) for placebo, p=<0.001.

There were 3 (0.5%) children in the palivizumab group and 9 (1.4%) in placebo who had a "nosocomial RSV hospitalization".
There was 1 (0.2%) child in the palivizumab group and 1 (0.2%) in placebo who died in the ER from RSV bronchiolitis; these deaths were included as RSV hospitalization endpoints.
A total of 5 children (3 palivizumab, 2 placebo) had more than one RSV hospitalization.

Sensitivity Analyses

The number of non-completers in the trial was small and balanced between treatment groups (Table 7). The distribution of specified categories of patient follow-up between the two treatment groups differed only with respect to RSV hospitalization (Kolmogorov-Smirnov analysis).

Table 7 Sponsor's Kolmogorov-Smirnov Analysis of RSV Hospitalization

	Palivizumab (n=639)		Placebo (n=648)	P-value [1]
No RSV Hospitalization – Completed Study	577	(90%)	556 (86%)	0.016
RSV Hospitalization	34	(5%)	63 (10%)	
No RSV Hospitalization – Premature Discontinuation or Death	28	(4%)	29 (5%)	

[1] P-value was based on the exact Kolmogorov-Smirnov test

Two sensitivity analyses were performed to assess impact of including possible RSV hospitalizations that did not meet the criteria for inclusion in the primary efficacy analysis. RSV hospitalization rates were adjusted to account for children with clinical illness consistent with RSV infection for whom

- no antigen test was done within the protocol specified testing window or
- there was virologic evidence of RSV infection but the child was excluded by case definition according to the protocol.

Children With No Antigen Test within the Protocol Specified Testing Window—

A small number of children did not have a protocol-required RSV antigen test done within 48 hours before or after hospital admission for an acute cardiorespiratory illness. Conventions to handle this were established before the study was unblinded. For this analysis, rate of RSV hospitalization for the alternative randomized group was used to estimate the impact of these children on the analysis of the primary endpoint. 14 (2%) children in the palivizumab group and 9 (1%) in placebo did not otherwise meet the primary endpoint and were hospitalized with evidence of a respiratory illness for which there was evidence of infection (coryza, fever or apnea), no alternative etiology and no RSV antigen test done within the protocol-specified testing window. Using this convention, 1 patient was added to the palivizumab group as having reached the primary endpoint and no patients were added to the placebo group. The result of this analysis (p=0.004) was similar to the result of the primary analysis (p=0.003).

Convention: Sensitivity analysis of RSV antigen test not done—

- Primary reason for hospital admission is cardiac/respiratory as defined on the admission CRF and there is evidence of cardiac/respiratory acute illness led by a cardiac/respiratory SAE
- No alternative diagnosis for the admission can be established

- Evidence of respiratory infection must be present
- RSV antigen test was never done or was negative and done outside the window for testing (48 hours before or after hospital admission)
- Has not otherwise met the primary endpoint

Children with Virologic Evidence of RSV Infection but Excluded by Case Definition—

3 children were hospitalized with lower respiratory tract infections and had virologic evidence (RSV culture or antigen test) of RSV but did not meet the protocol definition of RSV hospitalization. 2 of these patients had positive RSV antigen tests performed outside the allowable window. Patient #024301 (placebo) was hospitalized with bronchiolitis and a positive RSV antigen test obtained on hospital day 4. Patient #397304 (palivizumab) had a positive RSV antigen test obtained as an outpatient 6 days prior to admission with bronchopneumonia. Patient #010303 (placebo) had a positive RSV culture obtained at the time of hospitalization for acute bronchiolitis, but the RSV antigen test obtained at the same time was reported as negative. Analysis of the incidence of RSV hospitalizations was performed including these 3 patients as primary efficacy endpoints. The result of this analysis (p=0.002) was likewise similar to the result of the primary analysis (p=0.003).

Table 8 Sponsor's Sensitivity Analyses for RSV Hospitalization

	Palivizumab (n=639)		Placebo (n=648)		P-value [1]
Proportion Based on Inclusion of Patients with No Antigen Test per Convention					
RSV Hospitalization [2]	35	(6%)	63	(10%)	0.004
No RSV Hospitalization [3]	604	(95%)	585	(90%)	
Inclusion of 3 Cases with Virologic Evidence of RSV Infection but Excluded by Case Definition					
RSV Hospitalization [4]	35	(6%)	65	(10%)	0.002
No RSV Hospitalization [3]	604	(95%)	583	(90%)	

[1] P-value was obtained from Fisher's exact test.
[2] Adjusted rate for the number of children with (A) antigen test not done or (B) negative and done outside the window assuming a hospitalization rate equal to that of the other treatment group.
[3] The number of children who were not hospitalized for RSV plus the remaining children with non-RSV hospitalization who were not counted in the RSV hospitalization group.
[4] Adjusted rate including 3 cases with virologic evidence of RSV lower respiratory tract infection that did not meet protocol-defined case definition (1 case with + RSV culture/-RSV Ag; 2 cases with +RSV Ag but outside window).

Secondary Endpoints

The incidence of non-RSV hospitalization for any cause or for cardiac/respiratory causes was higher in the placebo group than in the palivizumab group (Table 9).

Table 9 Summary of Hospitalization

	Palivizumab (n=639)	Placebo (n=648)
Total N Hospitalizations	610	711
N Children With a Hospitalization For Any Cause		
Yes	351 (55%)	404 (62%)
No	288 (45%)	244 (38%)
N Children With a Hospitalization For Any Cause Except RSV		
Yes	342 (54%)	382 (59%)
No	297 (46%)	266 (41%)
N Children With a Cardiac/ Respiratory Hospitalization		
Yes	321 (50%)	359 (55%)
No	318 (50%)	289 (45%)
N Children With a RSV Hospitalization [1]		
Yes	34 (5%)	63 (10%)
No	605 (95%)	585 (90%)

[1] RSV hospitalization includes two RSV deaths outside the hospital. N=number.

The incidence of hospitalization was also examined by the stratification variable of cyanotic vs. non-cyanotic cardiac lesion.

Table 10 Summary of Hospitalizations by Cyanotic and Noncyanotic Strata

	Cyanotic Stratum		"Other" Stratum	
	Palivizumab	Placebo	Palivizumab	Placebo
Total N Hospitalizations	349	416	261	295
Total N Children	339	343	300	305
N Children With a Hospitalization For Any Cause	200 (59%)	226 (66%)	151 (50%)	178 (58%)
N Children With a Cardiac/ Respiratory Hospitalization	184 (54%)	202 (59%)	137 (46%)	157 (52%)
N Children With a RSV Hospitalization	19 (6%)	27 (8%)	15 (5%)	36 (12%)

Reviewer's comment: The incidence of RSV hospitalization was lower in the palivizumab group compared to placebo for both the cyanotic and non-cyanotic stratum. The incidence of all-cause hospitalization and cardiac-respiratory hospitalization were numerically highest in the cyanotic stratum assigned to placebo. However the incidence

of RSV hospitalization was numerically lower in this group than in the non-cyanotic placebo group.

An analysis was further performed to compare the secondary endpoints by treatment group in patients subgroups who had RSV hospitalization.

Table 11 Secondary Efficacy Endpoints: Summary of RSV Hospitalization

	Palivizumab (n=639)	Placebo (n=648)	% Reduction
Days of RSV Hospitalization			
Total Days	367	836	
Total Days/100 Children	57	129	56%
RSV Hospital Days of Increased Supplemental Oxygen Therapy			
Total Days	178	658	
Total Days/100 Children	28	102	73%
ICU Admission			
Yes	13 (2%)	24 (4%)	46%
Days of ICU Stay			
Total Days	101	461	
Total Days/100 Children	16	71	78%
Mechanical Ventilation			
Yes	8 (1%)	14 (2%)	41%
Days of Mechanical Ventilation			
Total Days	42	354	
Total Days/100 Children	7	55	88%

Reviewer's comment: The secondary endpoints appear to be consistent with the primary efficacy endpoint. All endpoints reflect lower number of days of RSV hospitalization and of respiratory support in the palivizumab arm than in the placebo arm. However analyses based on total days or total days normalized per 100 randomized patients are not readily interpretable; the analyses do not provide information on number of days per event. It should also be noted that the analyses are performed in subgroups of the randomized population.

The distribution of RSV hospital days in each study arm was skewed and an analysis based on total number of days is heavily influenced by a few patients with longer hospitalizations (≥21 days). FDA conducted a further analysis. The table below compares the days of RSV hospitalization between the two groups. The mean and median days in the palivizumab group and the placebo group show no statistically significant differences.

Table 12 Days of RSV Hospitalization Among Patients with RSV Hospitalization Incident

	Palivizumab	Placebo
N	34	63
Mean (SD)	10.8 (16.3)	13.3 (22.1)
Median	5.6	6.1
Percentile		
25% - 75%	3.7 – 9.9	2.8 – 13.7
10% - 90%	1.4 – 17.1	1.9 – 27.0
Range	0 – 81	0 -133

P = 0.5914 using Wilcoxon rank sum test

Reviewer's comment: These data suggest that RSV infection is not less severe in children who receive palivizumab than in children who receive placebo (as far as can be judged from children who are hospitalized). A similar interpretation was made from the data in the IMPACT study and that information is provided in the present product label.

Subgroup Analyses

Treatment Response by Cyanotic Status

The sponsor conducted a subgroup analysis by cyanotic status as stated in the statistical analytical plan. The study was not powered to assess treatment response in these subgroups. The treatment effect was numerically lower in the cyanotic stratum (Table 13). The Cochran-Mantel-Haenszel test was used to assess the treatment effect accounting for cardiac strata. The treatment effect was statistically significant when analyzed across strata (p=0.003). **Cyanotic placebo patients had a lower incidence of RSV hospitalization than non-cyanotic placebo patients.**

Table 13 Summary of Incidence of RSV Hospitalization by Stratum

	Palivizumab	Placebo		% Reduction	P-value [1]
Cyanotic Stratum	(n=339)	(n=343)			
RSV Hospitalization	19 (**6%**)	27	(**8%**)	29%	**0.285**
No RSV Hospitalization	320 (94%)	316	(92%)		
"Other" Stratum	(N=300)	(N=305)			
RSV Hospitalization	15 (**5%**)	36	(**12%**)	58%	**0.003**
No RSV Hospitalization	285 (95%)	269	(88%)		

[1] P-values were obtained from Fisher's exact test.

The Interactive Voice Response System (IVRS) was used to randomize patients into two strata-cyanotic or "other". CRF were used to confirm strata classification. Misclassifications were very few and had little or no effect on estimates of treatment response by stratum (not shown).

Results from the logistic regression analysis below show that age has a significant effect on RSV hospitalization. Older patients had lower incidence of RSV hospitalizations. Cyanotic stratum and gender had no effect on the treatment outcome.

Table 14 Logistic Regression of Incidence of RSV Hospitalization

	Parameter			**95% CI of Odds**
Variables	**Estimate**	**P-Value**	**Odds Ratio**	**Ratio**
Treatment (palivizumab)	-0.639	0.004	0.53	0.34-0.81
Stratum (cyanotic)	-0.212	0.324		
Gender (male)	-0.006	0.978		
Age	-0.069	0.004		

Reviewer's comment: The lower incidence of RSV hospitalization in placebo cyanotic patients might be due to a higher number of older (lower-risk) patients enrolled in this group. To explore this hypothesis the baseline demographics were examined by stratum and by treatment assignment and are shown in the tables below.

Table 15 Baseline Demographics by Cyanotic Strata (Based on CRF)in Combined Treatment Groups

	Cyanotic patients (n=690)	"Other" patients (n=597)
Sex		
Male	413 (60%)	280 (47%)
Female	277 (40%)	317 (53%)
Race		
Caucasian	477 (69%)	435 (73%)
Black	66 (10%)	47 (8%)
Hispanic	77 (11%)	66 (11%)
Asian	22 (3%)	14 (2%)
Other	48 (7%)	35 (6%)
Age at Study Entry (months)		
N	690	597
Mean (SD)	6.9 (5.6)	6.4 (5.4)
Median	5.4	4.6
Range	0.1-24.0	0–23.3
≤ 6 months	374 (54%)	367 (61%)
> 6 months	316 (46%)	230 (39%)
Weight at Study Entry (kg)		
N	689	595
Mean (SD)	6.1 (2.3)	5.9 (2.3)
Median	5.8	5.4
Range	2.2–14.0	2.0–13.4
Gestational Age (weeks)		
N	688	597
Mean (SD)	38.7 (1.9)	38.3 (2.4)
Median	39	39
Range	28-43	26-42
Multiple Birth		
Yes	29 (4%)	21 (4%)
No	661 (96%)	576 (96%)
Birth Weight		
N	688	595
Mean (SD)	3139 (592)	3009 (695)
Median	3180	3050
Range	980-5160	638-5000

Reviewer's comment: Comparing the baseline demographic by cyanotic strata it appears the median age at study entry was slightly older in cyanotic patients than that in the non-cyanotic patients, and the percentage of patients whose age is greater than 6 months was

higher in the cyanotic group compared to the non-cyanotic group. Male children predominate in the cyanotic strata and female children in the "other" stratum. Numbers in tables 15 and 16 differ between subgroups as stratification was based on either the CRF or IVRS.

Table 16 Baseline Demographics by Cyanotic Strata and by Treatment (Based on IVRS)

	Cyanotic Stratum		"Other" Stratum	
	Palivizumab	Placebo	Palivizumab	Placebo
Sex				
Male	205 (61%)	205 (60%)	144 (48%)	139 (46%)
Female	134 (40%)	138 (40%)	156 (52%)	166 (54%)
Race/Ethnicity				
Caucasian	235 (69%)	237 (69%)	218 (73%)	222 (73%)
Black	27 (8%)	39 (11%)	25 (8%)	22 (7%)
Hispanic	43 (13%)	32 (9%)	34 (11%)	34 (11%)
Asian	11 (3%)	12 (4%)	4 (1%)	9 (3%)
Other	23 (7%)	23 (7%)	19 (6%)	18 (6%)
Age at Study Entry (months)				
N	339	343	300	305
Mean (SE)	7 (0.3)	7 (0.3)	7 (0.3)	6 (0.3)
Median	5	6	5	5
Range	0.1-24	0.1-24	0.1-23	0-23
Weight at Study Entry				
N	339	342	299	304
Mean (SE)	6 (0.1)	6 (0.1)	6 (0.1)	6 (0.1)
Median	6	6	5	5
Range	2-14	2-13	2-13	2-13
Gestational Age (weeks)				
N	338	342	300	305
Mean (SE)	39 (0.1)	39 (0.1)	38 (0.1)	38 (0.1)
Median	39	39	39	39
Range	28-43	29-42	28-42	26-42
Multiple Birth				
Yes	11 (3%)	15 (4%)	16 (5%)	8 (3%)
No	328 (97%)	328 (96%)	284 (95%)	297 (97%)
Birth Weight (grams)				
N	339	341	298	305
Mean (SE)	3137 (32.5)	3139 (31.8)	2997 (41)	3027 (40)
Median	3175	3200	3062	3040
Range	980-5160	1180-4500	855-5000	638-4950

Reviewer's comment: Further examination of demographics by cardiac stratum and treatment assignment showed that all the variables were generally well balanced across

these subgroups. It was concluded that the demographic data in cyanotic patients assigned to placebo did not suggest that these children were at lower risk for severe manifestations of RSV infection.

Table 17 Incidence of RSV Hospitalization by Demographics and by Baseline RSV Antibody Status

	Palivizumab (n=639)	Placebo(n=648)	Relative Risk
Sex			
Male	14/349 (4%)	37/344 (11%)	0.37
Female	20/290 (7%)	26/304 (9%)	0.81
Age at Entry			
≤6 months	22/365 (6%)	46/376 (12%)	0.49
>6 months	12/274 (4%)	17/272 (6%)	0.70
Weight at Entry			
≤6 kg	24/365 (7%)	48/365 (13%)	0.50
>6 kg	10/273 (4%)	15/281 (5%)	0.69
Race			
Caucasian	21/453 (5%)	39/459 (9%)	0.55
Black	5/ 52 (10%)	5/ 61 (8%)	0.55
Hispanic	4/ 77 (5%)	10/ 66 (15%)	
Asian	1/ 15 (7 %)	1/ 21 (5 %)	
Other	3/ 42 (7%)	8/ 41 (20%)	
RSV Neutralizing Antibody at Entry			
< 1:200	22/372 (6%)	40/394 (10%)	0.58
≥ 1:200	7/170 (4%)	14/173 (8%)	0.51
Not Done	5/ 97 (5%)	9/ 81 (11%)	

Reviewer's comment: Under the race category, groups listed as Black and Asian note higher RSV hospitalization incidence on palivizumab vs. placebo, however numbers in these subgroups are too small to make any conclusions. In all other subgroups the incidence of RSV hospitalization appeared to be lower in the palivizumab group than in placebo. Age is an important parameter influencing RSV hospitalization; some treatment effect appears to remain in infants who are older than 6 months of age.

The incidence of RSV hospitalization was analyzed by study centers enrolling 20 or more patients as presented in the table below.

Table 18 RSV Hospitalization by Study Center (Sites Enrolling >=20 Patients)

Site number	Palivizumab RSV/Pts	Placebo RSV/Pts
001	0/22 (0%)	4/23 (17%)
002	1/19 (5%)	1/16 (6%)
010	1/13 (8%)	3/11 (27%)
014	2/20 (10%)	2/18 (11%)
015	1/16 (6%)	3/19 (16%)
020	1/10 (10%)	2/13 (15%)
021	0/15 (0%)	0/14 (0%)
022	0/23 (0%)	1/16 (6%)
024	3/21 (14%)	6/23 (26%)
025	0/9 (0%)	2/11 (18%)
028	0/15 (0%)	1/13 (8%)
029	2/11 (18%)	1/12 (8%)
070	0/10 (0%)	2/10 (20%)
072	3/9 (33%)	2/11 (18%)
091	0/13 (0%)	3/12 (25%)
122	1/7 (14%)	2/14 (14%)
187	1/19 (5%)	4/17 (24%)
397	0/17 (0%)	0/19 (0%)
399	0/10 (0%)	0/13 (0%)
402	0/12 (0%)	2/9 (22%)
422	1/12 (8%)	2/15 (13%)
424	0/10 (0%)	0/10 (0%)
434	0/16 (0%)	0/17 (0%)
435	1/12 (8%)	1/14 (7%)

Pts=patients.

The incidence of RSV hospitalization presented by all study center sites is located under Table 35 in the Appendix.

Reviewer's comment: Examination of treatment response by center showed treatment effect was apparent in the majority of the larger-enrolling centers.

Furthermore, the incidence of RSV hospitalization was examined by the various geographical regions where the study was conducted.

Table 19 Incidence of RSV Hospitalization by Region

	Palivizumab	**Placebo**
US (N=800)	(n=405)	(n=395)
RSV Hospitalization	24 (6%)	42 (11%)
Canada (N=133)	(N=66)	(N=67)
RSV Hospitalization	5 (8%)	8 (12%)
Europe (N=354)	(N=168)	(N=186)
RSV Hospitalization	5 (3%)	13 (7%)

Reviewer's comment: Treatment response was seen across the three regions.

The incidence of RSV hospitalization was further examined by the year the study was conducted as shown in the table below.

Table 20 Summary of Incidence of RSV Hospitalization by Study Year

	Palivizumab		Placebo	
Year of Study	(n=639)		(n=648)	
Year 1	8/125	(6%)	17/123	(14%)
Year 2	14/223	(6%)	16/227	(7%)
Year 3	8/176	(5%)	18/179	(10%)
Year 4	4/115	(4%)	12/119	(10%)

Reviewer's comment: In each year of the study, the incidence of RSV hospitalization was lower in the palivizumab group than in placebo (Table 20). During each of the 4 years of the study, hospitalizations for RSV were highest in December, January and February, consistent with the typical seasonal epidemiology of RSV infection in the Northern Hemisphere (Table 21).

The incidence of RSV hospitalization was examined by each particular month of study as shown in the table below.

Table 21 Summary of Incidence of RSV Hospitalization by Month For Years 1-4 Combined

	Palivizumab		Placebo	
	(n=639)		(n=648)	
Total RSV Hospitalizations [1]				
November	1	(0%)	4	(1%)
December	9	(1%)	15	(2%)
January	8	(1%)	20	(3%)
February	8	(1%)	14	(2%)
March	4	(1%)	7	(1%)
April	4	(1%)	2	(0%)
May	0	(0%)	1	(0%)

[1] Children with more than one RSV hospitalization were counted in the month in which the first hospitalization occurred. Children with a "nosocomial RSV hospitalization" were counted in the month of onset of the "nosocomial RSV hospitalization."

The total number of RSV hospitalizations is shown in the table below by each month on the study for the treatment groups.

Table 22 Number of RSV Hospitalizations by Treatment Group by Month on Study

Days	Month on Study	Palivizumab (n=639)	Placebo (n=648)
<=30	1	10 (2%)	18 (3%)
<30-60	2	8 (1%)	15 (2%)
>60-90	3	9 (1%)	19 (3%)
>90-120	4	4 (1%)	6 (1%)
>120-150	5	3 (1%)	5 (1%)

Reviewer's comment: Fewer RSV hospitalizations occurred in the palivizumab group compared to placebo for each month of study participation.

Concomitant Medications

Overall use of concomitant medications in the two study arms was similar for the following drug classes: antimicrobial, corticosteroids, cardiac, respiratory, analgesics and antipyretic. The use of ribavirin and parenterally or orally administered steroids to patients hospitalized with RSV lower respiratory tract infection (RSV hospitalizations) was analyzed. The use of these agents during an RSV hospitalization appeared to be lower in the palivizumab group (1.4%) than in placebo (3.2%). Table 23 shows usage of corticosteroids and antivirals during the study.

Table 23 Selected Concomitant Medications

Drug Class	**Palivizumab** (n=639)		**Placebo** (n=648)	
Steroids				
Dexamethasone	61	(10%)	83	(13%)
Hydrocortisone	38	(6%)	58	(9%)
Methylprednisolone	67	(11%)	79	(12%)
Antivirals				
Ribavirin	2	(0%)	3	(1%)

The table below presents patients with RSV hospitalization receiving ribavirin or steroids. There was no difference in the use of these drugs in children with RSV hospitalization.

Table 24 Use of Ribavirin and/or Steroids in Children Hospitalized With RSV Infection

	Palivizumab (n=639)	**Placebo** (n=648)
Total Number of Children With RSV Hospitalization	34	63
Total Number of Children Receiving One or More Doses of	9 (23%)	21 (33%)
Ribavirin	1 (3%)	3 (5%)
Oral steroids [1]	2 (6%)	6 (10%)
Parenteral steroids [2]	7 (21%)	14 (22%)

[1] Prednisone
[2] Dexamethasone, hydrocortisone, methylprednisolone

Serum Palivizumab Concentrations

In the IMPACT trial the mean half-life of palivizumab was 20 days and after the first dose mean (±SD) 30-day trough concentration was 37±21 mcg/ml with progressive accumulation to 72±50 mcg/ml. In the CHD trial the mean 30-day troughs after the first and fourth injection were respectively 56 and 91 mcg/ml. The mean body weight (MBW±SE) at entry for IMPACT trial was 4.9±0.1 kg for placebo and 4.8±0.07 kg for palivizumab and the mean age at entry was 6±0.21 months for placebo and 5.7±0.15 months for palivizumab. For the CHD trial, the MBW at entry was 6.0±0.1 kg for placebo and 6.1±0.1 kg for palivizumab and the mean age at entry was 6.5±0.2 months for placebo and 6.8± 0.2 months for palivizumab.

To assess the impact of cardiac bypass on serum palivizumab concentrations, serum was obtained prior to and following cardiac bypass. Paired pre- and post-bypass serum palivizumab levels were available for analysis for 139 patients in the palivizumab group and 135 patients in the placebo group. Prior to bypass, the mean serum palivizumab concentration was 98.0 μg/mL in the palivizumab group. Following bypass, the mean serum level was 41.4 μg/mL in the palivizumab group (a reduction of 58%).

Table 25 Serum Palivizumab Concentrations For Patients Who Underwent Cardiac Bypass

	Palivizumab
	(n=639)
Total N Bypass Surgeries	190
Pre-Bypass Surgery [1]	
N	139
Mean	98.0
CV	52.7
Median	93.2
Range	(0.0-364.0)
Post-Bypass Surgery [1]	
N	139
Mean	41.4
CV	80.0
Median	37.4
Range	(0.0-303.0)

[1] Only those patients who had paired pre- and post-bypass serum samples available were analyzed.

Palivizumab concentration mcg/ml	N	%
Serum Palivizumab Concentrations For Patients pre-Cardiac Bypass		
<30	7	5.0
30-70	35	25.2
>70	97	69.8
Serum Palivizumab Concentrations For Patients post-Cardiac Bypass		
<30	55	39.6
30-70	69	49.6
>70	15	10.8
Total	139	100

Approximately 40% of patients had palivizumab levels lower than 30 mcg/ml post-operatively.

The potential clinical significance of the post-CPB drop in palivizumab serum levels was assessed by examining drug levels in patients who underwent RSV hospitalization. In the Impact trial mean serum palivizumab concentrations were 84 mcg/ml in the 48 active arm patients who underwent an RSV hospitalization (see medical officer review). In the CHD trial of the 33 RSV hospitalizations for which sera were obtained only 3 of the hospitalizations had serum palivizumab <30 mcg/ml. These data do not suggest that levels of palivizumab are predictive of RSV hospitalization risk. The data also do not suggest that the 30 mcg/ml level is a treatment failure threshold.

Examination of RSV hospitalization by month on study does not show a relationship between reduction of risk and month on study. This suggests lack of dose response in the range of 50-100 mcg/ml palivizumab.

The EMEA label recommends redosing (15 mg/kg) children who undergo cardiopulmonary bypass. This recommendation is endorsed by the American Academy of Pediatrics. The DOSAGE AND ADMINISTRATION section of the proposed revised label recommends redosing post bypass.

Reviewer's comment: There is no evidence that the post-CPB reduction in palivizumab plasma level will affect efficacy. There are no significant concerns with safety of an additional dose of palivizumab administered before the scheduled next dose. It is reasonable to replace the loss of drug resulting from the surgical procedure.

Safety Analyses

Incidence of adverse events was similar in the palivizumab and placebo groups (96% palivizumab and 97% placebo). Findings were similar when adverse events were analyzed by cardiac stratum (cyanotic or "other").

The incidence of adverse events judged to be related to study treatment (7% palivizumab, 7% placebo) and the incidence of events that required medical intervention (92% palivizumab, 93% placebo) were similar in the two study groups. No child had study drug discontinued for a related adverse event.

Incidence of serious adverse events was numerically lower in the palivizumab group than in the placebo group (55% versus 63%,). The incidences of cardiac surgeries classified as planned, earlier than planned, or urgent were similar between treatment groups.

Deaths: A total of 48 children died during the study, 21 (3%) in the palivizumab group and 27 (4%) in the placebo group. No deaths were attributed to study drug. Deaths associated with RSV infection occurred in 2 patients in the palivizumab group and 4 patients in the placebo group.

The incidence of fever, infection, injection site reaction, conjunctivitis, arrhythmia, cyanosis and URI was > 1% higher (1 to 4%) in the palivizumab group than placebo (see shaded terms).

Table 26 Incidence of Preferred Terms

Preferred Term	Palivizumab (n=639)		Placebo (n=648)	
URI	303	(47.4%)	299	(46.1%)
Heart malformation	216	(33.8%)	231	(35.6%)
Otitis media	177	(27.7%)	197	(30.4%)
Fever	173	(27.1%)	155	(23.9%)
Rash	163	(25.5%)	175	(27.0%)
Rhinitis	151	(23.6%)	165	(25.5%)
Diarrhea	124	(19.4%)	123	(19.0%)
Gastroenteritis	101	(15.8%)	107	(16.5%)
Vomiting	92	(14.4%)	100	(15.4%)
Pain	78	(12.2%)	75	(11.6%)
Cough	76	(11.9%)	91	(14.0%)
Conjunctivitis	72	(11.3%)	60	(9.3%)
RSV	58	(9.1%)	86	(13.3%)
Cyanosis	58	(9.1%)	45	(6.9%)
Nervousness	56	(8.8%)	73	(11.3%)
Pneumonia	48	(7.5%)	64	(9.9%)
Constipation	43	(6.7%)	46	(7.1%)
Viral infection	41	(6.4%)	48	(7.4%)
Pharyngitis	40	(6.3%)	52	(8.0%)
Gastrointestinal Disorder	40	(6.3%)	39	(6.0%)
Pleural Effusion	36	(5.6%)	42	(6.5%)
Infection	36	(5.6%)	19	(2.9%)
Bronchiolitis	34	(5.3%)	47	(7.3%)
Anemia	32	(5.0%)	39	(6.0%)
Wheeze	32	(5.0%)	33	(5.1%)
Feeding Abnormalities	31	(4.9%)	30	(4.6%)
Oral moniliasis	31	(4.9%)	48	(7.4%)
Bronchitis	30	(4.7%)	31	(4.8%)
Congestive Heart Failure	28	(4.4%)	34	(5.2%)
Respiratory Disorders	26	(4.1%)	26	(4.0%)
Failure to Thrive	25	(3.9%)	21	(3.2%)
Infection Bacterial	25	(3.9%)	25	(3.9%)
Dyspnea	25	(3.9%)	23	(3.5%)
Urinary Tract Infection	24	(3.8%)	27	(4.2%)
Accidental Injury	22	(3.4%)	31	(4.8%)
Study Drug Injection Site Reaction	22	(3.4%)	14	(2.2%)
Atelectasis	22	(3.4%)	17	(2.6%)
Hypoxia	22	(3.4%)	35	(5.4%)
Hemorrhage	21	(3.3%)	17	(2.6%)
Arrhythmia	20	(3.1%)	11	(1.7%)
Hypokalemia	20	(3.1%)	22	(3.4%)
Heart failure	19	(3.0%)	26	(4.0%)
Flu Syndrome	15	(2.3%)	11	(1.7%)
Sepsis	14	(2.2%)	17	(2.6%)
Fungal Dermatitis	14	(2.2%)	17	(2.6%)
Somnolence	13	(2.0%)	8	(1.2%)
Lung Edema	13	(2.0%)	9	(1.4%)

Sinusitis	13	(2.0%)	14	(2.2%)
Eczema	13	(2.0%)	16	(2.5%)
Cardiovascular Disorder	12	(1.9%)	12	(1.9%)
Pericardial Effusion	12	(1.9%)	17	(2.6%)
Infection Fungal	11	(1.7%)	10	(1.5%)
Tachycardia	11	(1.7%)	13	(2.0%)
Croup	11	(1.7%)	9	(1.4%)
Edema	9	(1.4%)	8	(1.2%)
Overdose	9	(1.4%)	4	(0.6%)
Bradycardia	9	(1.4%)	8	(1.2%)
Pulmonary Hypertension	9	(1.4%)	10	(1.5%)
Apnea	9	(1.4%)	7	(1.1%)
Pneumothorax	9	(1.4%)	9	(1.4%)
Ear disorder	9	(1.4%)	12	(1.9%)
Injection Site Reaction, Other	8	(1.3%)	9	(1.4%)
Flatulence	8	(1.3%)	10	(1.5%)
Hyperventilation	8	(1.3%)	12	(1.9%)
Coagulation Disorder	7	(1.1%)	7	(1.1%)
Thrombocytopenia	7	(1.1%)	16	(2.5%)
Stridor	7	(1.1%)	11	(1.7%)

URI=upper respiratory tract infection.

The incidence of fever, infection, injection site reaction, arrhythmia, cyanosis and URI was further examined by attribution of causality and by seriousness as shown in the table below.

Table 27 Preferred Terms with Incidence >=1% *Higher* in the Palivizumab Group

	Palivizumab (n=639)		Placebo (n=648)		Difference in Rate
Body as Whole					
Fever	173	(27.1%)	155	(23.9%)	3.2%
Related	11	(1.7%)	10	(1.5%)	
Serious	5	(0.8%)	9	(1.4%)	
Serious and Related	0	(0.0%)	1	(0.2%)	
Infection	36	(5.6%)	19	(2.9%)	2.7%
Related	0	(0.0%)	0	(0.0%)	
Serious	2	(0.3%)	4	(0.6%)	
Serious and Related	0	(0.0%)	0	(0.0%)	
Study Drug Injection Site Reaction	22	(3.4%)	14	(2.2%)	1.2%
Related	17	(2.7%)	13	(2.0%)	
Serious	0	(0.0%)	0	(0.0%)	
Serious and Related	0	(0.0%)	0	(0.0%)	
Cardiovascular System					
Arrhythmia	20	(3.1%)	11	(1.7%)	1.4%
Related	0	(0.0%)	0	(0.0%)	
Serious	1	(0.2%)	2	(0.3%)	
Serious and Related	0	(0.0%)	0	(0.0%)	
Cyanosis	58	(9.1%)	45	(6.9%)	2.2%
Related	0	(0.0%)	1	(0.2%)	
Serious	23	(3.6%)	14	(2.2%)	
Serious and Related	0	(0.0%)	1	(0.2%)	
Respiratory System					
URI	303	(47.4%)	299	(46.1%)	1.3%
Related	2	(0.3%)	1	(0.2%)	
Serious	31	(4.9%)	25	(3.9%)	
Serious and Related	0	(0.0%)	0	(0.0%)	

Injection Site Reaction: Study drug site of injection reactions were reported in 22 (3.4%) patients in the palivizumab group and 14 (2.2%) patients in placebo. There were no serious adverse events coded to study drug injection site reaction for either treatment group. The most common injection site reactions were redness, swelling and bruising at the site of injection. There were 4 patients in the palivizumab group and 1 in placebo in whom injection site reactions occurred after more than one injection, and none in which they were reported after more than two injections.

Allergic Reactions: Allergic reactions were uncommon. They occurred in 3 (0.5%) patients on palivizumab and 10 (1.5%) on placebo. No allergic reactions were attributed to the drug on either treatment group. Allergic reactions reported were attributed to antibiotics (5 on placebo), environmental allergens (3 total, 1 on placebo), narcotic analgesics (2 on placebo) and food (1 on placebo). Two allergic reactions were serious, both being in the palivizumab group. Of those, one was due to an intravenous contrast dye and the other was a metoclopramide (Reglan) drug reaction.

The agency further requested all adverse events occurring in both of trials, the IMPACT trial with patients with bronchopulmonary dysplasia and premature birth and the CHD trial, be pooled together. Review of the adverse event data after pooling (data not shown) revealed no additional safety signals.

The tables below show adverse events that occurred at a frequency of greater than 1% of the patients on the palivizumab group compared to the placebo group in the IMPACT trial, in the CHD trial and in the combined safety database from both trials.

The table below presents the adverse events occurring in the first IMPACT trial at a frequency greater than 1% in the palivizumab group compared to placebo.

Table 28 Adverse Events Occurring in IMPACT-RSV Trial at a Frequency of >1% in Palivizumab Compared to Placebo

Reported Adverse Events	Palivizumab n=1002	Placebo n=500
Upper respiratory infection	53%	49%
Otitis media	42%	40%
Rhinitis	29%	23%
Rash	26%	22%
Pain	9%	7%
Hernia	6%	5%
SGOT increased	5%	4%
Pharyngitis	3%	1%

The table below presents the adverse events occurring in the second CHD trial at a frequency greater than 1% in the palivizumab group compared to placebo.

Table 29 Adverse Events Occurring in Congential Heart Disease (CHD) Trial at a Frequency of >1% in Palivizumab Compared to Placebo

Reported Adverse Events	Palivizumab n=639	Placebo n=648
Upper respiratory infection	47%	46%
Fever	27%	24%
Conjunctivitis	11%	9%
Cyanosis	9%	7%
Infection	6%	3%
Study Drug Injection Site Reaction	3%	2%
Arrhythmia	3%	2%

The table below displays the adverse events pooled from both trials.

Table 30 Adverse Events Occurring at a Frequency of >1% in Palivizumab Compared to Placebo in IMPACT-RSV and CHD Trials Combined

Reported Adverse Events	Palivizumab n=1641	Placebo n=1148
Upper respiratory infection	830 (51%)	544 (47%)
Otitis media	597 (36%)	397 (35%)
Fever	445 (27%)	289 (25%)
Rhinitis	439 (27%)	282 (25%)
Wheeze	170 (10%)	100 (9%)
Hernia	68 (4%)	30 (3%)
SGOT increased	49 (3%)	20 (2%)

Reviewer's comment: Recommend that the label present pooled adverse reaction data. The appearance of the term " (b) (4) *in the pooled table is a consequence of pooling studies with different randomization ratios and different background event rates.* (b) (4) *was not higher in the palivizumab group in either IMPACT or CHD trial analyzed alone.*

The table below presents the fatalities occurring in both treatment groups.

Table 31 Summary of Fatalities

	Palivizumab	Placebo
	(n=639)	(n=648)
Total Number of Fatalities	21	27
Respiratory Disease Related	2 (0.3%)	2 (0.3%)
Sudden Death	5 (0.8%)	8 (1.2%)
Cardiac Surgery Related	6 (0.9%)	5 (0.8%)
Other	8 (1.3%)	12 (1.9%)
Fatalities Considered Related to Study Drug	0 (0.0%)	0 (0.0%)
Fatalities Associated with RSV	2 (0.3%)	4 (0.6%)
Fatalities by Randomization Strata		
Cyanotic	11 (1.7%)	19 (2.9%)
"Other"	10 (1.6%)	8 (1.2%)

Reviewer's comment: The incidence of death from all causes and from respiratory (including RSV) events was similar in the two groups.

The table below presents the total number of serious adverse events occurring in the entire patient population.

Table 32 Summary of Serious Adverse Events (Total Population)

	Palivizumab		Placebo	
Body System	**(n=639)**		**(n=648)**	
Total Number of Events	748		859	
Total Number of Children Reporting One or More Event	354	(55.4%)	409	(63.1%)
Body as Whole	55	(8.6%)	64	(9.9%)
Cardiovascular System	252	(39.4%)	274	(42.3%)
Digestive System	65	(10.2%)	72	(11.1%)
Hemic and Lymphatic System	5	(0.8%)	5	(0.8%)
Metabolic and Nutritional Disorders	4	(0.6%)	9	(1.4%)
Musculoskeletal	2	(0.3%)	1	(0.2%)
Nervous System	10	(1.6%)	11	(1.7%)
Respiratory System	144	(22.5%)	177	(27.3%)
Skin and Appendages	2	(0.3%)	2	(0.3%)
Special Senses	3	(0.5%)	4	(0.6%)
Urogenital System	11	(1.7%)	12	(1.9%)

Reviewer comment: The incidence of serious adverse events was 54% in the palivizumab group and 63% in the placebo group. The incidence by body system was also similar in the two groups.

Also, analyzed were the number of patients having cardiac surgical procedures including interventional catheterization.

Table 33 Summary of Cardiac Surgery/Interventional Catheterization (Total Population)

	Palivizumab (n=639)	Placebo (n=648)
Total N Procedures		
Planned	190	214
Earlier Than Planned	40	39
Urgent	22	27
N Children Having Procedures		
None	421 (66%)	410 (63%)
Planned	164 (26%)	186 (29%)
Earlier Than Planned	34 (5%)	34 (5%)
Urgent	20 (3%)	18 (3%)

Reviewer's comment: The number of cardiac surgery and other interventions were similar between groups.

Trial Conduct

Interim Analyses

The DSMB reviewed the safety data annually and performed an interim analysis after 698 patients representing approximately 54% of the total number of patients had completed the study. The DSMB made no recommendations to alter the conduct of the trial.

Stratification Errors

7 (1.1%) patients in the palivizumab group and 7 (1.1%) patients in the placebo group were stratified incorrectly at the time of randomization. 11 patients with heart lesions classified in the CRFs as belonging to the cyanotic stratum were entered incorrectly into the IVRS as belonging to the "other" stratum. Three patients with heart lesions classified in the CRFs as category 9 ("other" stratum) were entered incorrectly into the IVRS as one of categories 1 through 8 (cyanotic stratum). Two patients (#02402 and #001109) who were stratified incorrectly met the primary endpoint of RSV hospitalization. Patient #02402 was stratified incorrectly to the cyanotic stratum and Patient #001109 was stratified incorrectly to the "other" stratum.

Classification Errors

4 (0.6%) patients in the placebo group and 1 (0.2%) patient in the palivizumab group were classified incorrectly within the cyanotic stratum. None of these patients had an RSV hospitalization endpoint.

Financial Disclosure

None of the investigators had a financial interest in the trial as defined in 21 CFR 54.2 at the time the study database was frozen on July 30, 2002. One principal investigator at site 222/251, as of August 7, 2003, is noted to exceed the 21 CFR 54.2 limit. This investigator enrolled 16 patients in the trial. Nine patients were in the palivizumab group and 7 patients were in placebo. No child from this investigator's study site had a RSV hospitalization.

Summary of Efficacy

A total of 34 (5.3%) of the 639 children in the palivizumab group met the primary endpoint of RSV hospitalization compared to 63 (9.7%) of the 648 children in the placebo group (p=0.003; Fisher's exact test). This represents a 45% relative reduction in the incidence of RSV hospitalization among children receiving palivizumab prophylaxis. Non-completers were balanced between the treatment groups and the result of sensitivity analyses (including children with respiratory hospitalizations for whom an RSV antigen test was not performed and children hospitalized with virologic evidence for RSV but who did not meet the protocol defined criteria for RSV hospitalization) supported the evidence of treatment effect. Treatment effect was consistent over time, across geographic regions, across cardiac strata, and within subgroups of children defined by gender, age, weight, race, and presence of RSV neutralizing antibody at entry. All secondary efficacy endpoints showed reductions in the palivizumab group compared to placebo. No results of this study suggest that RSV infection is less severe in palivizumab-treated patients than placebo patients among those patients who undergo RSV hospitalization.

Summary of Safety

Incidence of adverse events was similar in the palivizumab and placebo groups (96% palivizumab and 97% placebo). Findings were similar when adverse events were analyzed by cardiac stratum (cyanotic or "other"). The incidence of adverse events judged to be related to study treatment (7% palivizumab, 7% placebo) and the incidence of events that required medical intervention (92% palivizumab, 93% placebo) were similar in the two study groups. One child had study drug discontinued due to an adverse event.

Those preferred terms with an incidence >=1% higher (range 1.2%–3.2%) in the palivizumab group than in the placebo group included fever, infection, study drug injection site reaction, URI, conjunctivitis, arrhythmia, and cyanosis. Serious adverse events do not raise any special concerns for palivizumab-treatment. The incidences of cardiac surgeries classified as planned, earlier than planned, or urgent were similar between treatment groups.

Deaths: A total of 48 children died during the study, 21 (3%) in the palivizumab group and 27 (4%) in the placebo group. No deaths were attributed to study drug. Deaths associated with RSV infection occurred in 2 patients in the palivizumab group and 4 patients in the placebo group. Deaths attributed to acute respiratory disease, 2 were palivizumab and 2 placebo. Of 13 sudden deaths, 5 were on palivizumab and 8 placebo. Six deaths on palivizumab and 5 placebo were associated with cardiac surgery. Among fatalities due to other causes, 8 were on palivizumab and 12 placebo.

CONCLUSION

Palivizumab at its indicated dose of 15 mg/kg is safe and effective for prophylaxis of serious RSV illness in infants and children <=2 years of age with congenital heart disease.

RECOMMENDED REGULATORY ACTION

We recommend the use of palivizumab for prophylaxis of RSV for children <=2 years with significant congential heart disease be granted.

APPENDIX

Table 34 Table of Study Procedures

	Routine Visits						Hospitalization	
	Study Day 0	**Study Day 30**	**Study Day 60**	**Study Day 90**	**Study Day 120**	**Study Day 150**	**Cardio/ Resp**	**Other**
Informed Consent	X							
History and Physical Exam	X	X	X	X	X	X	X	X
Cardiovascular Assessment	X	X	X	X	X	X	X	X
Serum RSV Neut Ab Titer	X							
RSV Antigen Test							X [2,3]	X [3]
Serum Palivizumab	X	X			X		X [1]	
Reserve Sample (serum)	X	X			X		X	
Hospitalization Record							X	X
Study Drug Injection	X	X	X	X	X			

[1] Blood for determination of serum palivizumab concentration was to be obtained on admission. In addition, if cardiopulmonary bypass was used during surgery, serum for palivizumab concentration was to be obtained before bypass and on the day following bypass.
[2] RSV antigen testing was to be performed at the time of each cardiorespiratory admission (other than an admission for a planned surgical procedure or an admission for diagnostic testing not associated with an acute illness).
[3] For all hospitalizations, RSV antigen testing was to be performed whenever cardiac/respiratory deterioration occurred during hospitalization.

Table 35 Incidence of RSV Hospitalization By Site

Site Number	Palivizumab RSV/Pts	(%)	Placebo RSV/Pts	(%)
001	0/22	(0%)	4/23	(17%)
002	1/19	(5%)	1/16	(6%)
003	0/10	(0%)	2/9	(22%)
004	1/7	(14%)	0/8	(0%)
006	1/11	(9%)	0/7	(0%)
008	0/7	(0%)	1/8	(13%)
009	1/6	(17%)	0/6	(0%)
010	1/13	(8%)	3/11	(27%)
011	2/6	(33%)	0/6	(0%)
013	0/1	(0%)	1/2	(50%)
014	2/20	(10%)	2/18	(11%)
015	1/16	(6%)	3/19	(16%)
017	0/3	(0%)	0/2	(0%)
018	0/8	(0%)	0/7	(0%)
019	1/3	(33%)	0/2	(0%)
020	1/10	(10%)	2/13	(15%)
021	0/15	(0%)	0/14	(0%)
022	0/23	(0%)	1/16	(6%)
023	0/4	(0%)	0/ 4	(0%)
024	3/21	(14%)	6/23	(26%)
025	0/9	(0%)	2/11	(18%)
026	0/7	(0%)	1/7	(14%)
027	1/5	(20%)	0/5	(0%)
028	0/15	(0%)	1/13	(8%)
029	2/11	(18%)	1/12	(8%)
062	0/9	(0%)	0/5	(0%)
070	0/10	(0%)	2/10	(20%)
072	3/9	(33%)	2/11	(18%)
091	0/13	(0%)	3/12	(25%)
095	0/5	(0%)	1/6	(17%)
121	0/8	(0%)	1/10	(10%)
122	1/7	(14%)	2/14	(14%)
183	0/5	(0%)	1/6	(17%)
187	1/19	(5%)	4/17	(24%)
194	1/ 9	(11%)	0/10	(0%)
197	0/2	(0%)	0/2	(0%)
222	0/2	(0%)	0/3	(0%)
239	0/11	(0%)	1/7	(14%)
251	0/7	(0%)	0/4	(0%)
266	0/0	(0%)	0/1	(0%)
275	0/6	(0%)	0/3	(0%)
396	0/8	(0%)	0/6	(0%)
397	0/17	(0%)	0/19	(0%)
398	0/6	(0%)	2/8	(25%)
399	0/10	(0%)	0/13	(0%)
401	0/3	(0%)	0/2	(0%)

402	0/12	(0%)	2/9	(22%)
403	0/3	(0%)	1/3	(33%)
404	0/3	(0%)	0/3	(0%)
405	2/10	(20%)	1/9	(11%)
406	0/1	(0%)	0/1	(0%)
407	0/4	(0%)	0/7	(0%)
408	0/4	(0%)	0/7	(0%)
409	0/1	(0%)	0/4	(0%)
410	0/10	(0%)	1/8	(13%)
411	0/2	(0%)	0/3	(0%)
412	0/2	(0%)	0/1	(0%)
413	0/4	(0%)	0/2	(0%)
414	0/5	(0%)	1/6	(17%)
415	0/6	(0%)	0/9	(0%)
416	0/2	(0%)	0/6	(0%)
417	1/10	(10%)	0/8	(0%)
418	0/4	(0%)	1/4	(25%)
419	1/5	(20%)	0/9	(0%)
420	1/8	(13%)	1/9	(11%)
421	0/7	(0%)	1/8	(13%)
422	1/12	(8%)	2/15	(13%)
424	0/10	(0%)	0/10	(0%)
425	1/2	(50%)	0/3	(0%)
426	0/8	(0%)	0/8	(0%)
427	1/10	(10%)	0/9	(0%)
433	0/8	(0%)	0/8	(0%)
434	0/16	(0%)	0/17	(0%)
435	1/12	(8%)	1/14	(7%)
436	0/12	(0%)	1/13	(8%)
603	0/5	(0%)	0/4	(0%)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

9/8/03

ADDENDUM

STN Number: 103770/5033
Product Name: Synagis (Palivizumab)
Submission Dates: 11/14/02, 3/24/03, 7/28/03, 8/8/03

The clinical pharmacology review for this submission was signed off (dated on May 8, 2003). Additional questions were raised later regarding the need for dosage adjustment in patients undergoing cardiopulmonary by-pass for open-heart surgery. The sponsor responded these questions through the fax on July 28, 2003 and the email on August 8, 2003.

The sponsor is requested to provide the dose ranging studies that demonstrated the 30 μg/ml palivizumab serum concentration being the effective trough concentration. According to the sponsor, in cotton rat experiments with palivizumab, a mean reduction in pulmonary RSV titter of 99% was achieved at serum levels of 25-30 μg/ml and all animals with serum levels above 40 μg/ml had at least a 2 log reduction in pulmonary RSV titer. In human pharmacokinetic studies, mean 30-day trough serum levels ≥30 μg/ml were achieved by a dose of 15 mg/kg. This dose was used in subsequent successful Phase III trials (the Impact-RSV and the Congenital Heart Disease (CHD) trials) of palivizumab for the reduction in RSV hospitalizations in premature infants, infants with bronchopulmonary dysplasia, and hemodynamically significant congenital heart disease. Although 30 μg/ml trough levels were used to determine dose and dose regimen of palivizumab, efficacy trials were not conducted with other doses or targeted serum trough levels to definitively demonstrate the threshold of protection.

To the question that how many by-pass patients had <30 μg/ml levels after surgery, the answer is that about 40% (n=55) with levels <30 μg/ml, 50% (n=69) with levels between 30 to 70 μg/ml and 10 % (n=15) with levels >70 μg/ml. There were 139 cardiac by-pass surgery events in the palivizumab group for which both pre and post procedure serum samples were obtained. These events occurred in 135 children; 2 children had 2 by-pass procedures. In the CHD trial, mean trough serum palivizumab concentrations after the first and fourth palivizumab injections were 55.5 μg/ml and 90.8 μg/ml, respectively. Thus, the low post by-pass serum palivizumab concentrations observed suggest that re-dosing of children after by-pass surgery would be indicated to return serum levels above the mean trough levels.

In regard to the correlation of individual palivizumab serum concentrations with clinical outcome (individual protection against RSV hospitalizations), it was found problematic due to variable timing of pre-hospitalization RSV illness and RSV hospitalization relative to scheduled palivizumab dosing. Confounders to the analysis include small numbers of subjects, missing data, and variability in the timing of RSV exposure and dosing.

Given that 1) it has been established that maintaining the target levels of serum palivizumab by giving 15 mg/kg of palivizumab monthly is effective, 2) the levels fall by 58% post-bypass, and 3) in practice children will not have palivizumab levels measured,

it is appropriate to recommend that a 15 mg/kg injection of palivizumab be administered as soon as a child is stable after surgery to ensure adequate palivizumab serum levels in children immunoprophylaxed with palivizumab. Subsequently, palivizumab should be dosed monthly through the remainder of the RSV season for children that continue to be at high risk of RSV disease.

The following wording for the Dosing and Administration section of labeling is proposed by the sponsor:

(b) (4)

[redacted]

According to the sponsor, recently the American Academy of Pediatrics Committee on Infectious Diseases (Redbook 26th edition, 2003) recommended the following: "Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab (15 mg/kg) should be considered as soon as the patient is medically stable." The language recently accepted by the EMEA is as follows: "For children undergoing cardiac bypass, it is recommended that a 15 mg/kg injection of palivizumab be administered as soon as stable after surgery to ensure adequate palivizumab serum levels. Subsequent doses should resume monthly through the remainder of the RSV season for children that continue to be at high risk of RSV disease".

(b) (4)

[redacted]

(b) (4)

[redacted]

Hong Zhao 9/8/03

Hong Zhao, Ph.D.
Clinical Pharmacology Reviewer

Martin D. Green 9/8/03

Martin David Green, Ph.D.
Branch Chief, Clinical Pharmacology and Toxicology

5/8/03

Clinical Pharmacology Review Worksheet

Submission Date: 11/14/02, 3/24/03

STN Number:	10-3770/5033
Product Name:	Synagis® (Palivizumab), Humanized Monoclonal Antibody to F-protein of Respiratory Syncytial Virus (RSV)
Dosage Form:	Sterile Lyophilized Product, 50 mg/vial and 100 mg/vial, Intramuscular Injection
Indication:	For the prevention of serious lower respiratory tract disease, caused by RSV, in infants and children with bronchopulmonary dysplasia (BPD) or a history of premature birth (≤35 weeks gestation) [redacted] (b) (4)
Submission Type:	Efficacy Supplement
Sponsor:	MedImmune, Inc., Gaithersburg, MD
Related INDs:	BB-IND 5862; BLA 97-1359, License #1252
Reviewer:	Hong Zhao, Ph.D.

Introduction

This is an efficacy supplement providing the final study report for the phase 3 clinical trial, MI-CP048, entitled "A Study of the Safety, Tolerance, and Efficacy of Palivizumab (MEDI-493, Synagis) for Prophylaxis of Respiratory Syncytial Virus in Children with Congenital Heart Disease". The study was conducted under BB-IND 5862. Based on the results of the study, the sponsor proposes to modify the package insert as follows (sentences in italic are the proposed additions):

Under CLINICAL PHARMACOLOGY section, the following statements are added to [redacted] (b) (4)

The efficacy result of CHD Study is added to the CLINICAL STUIDIES section and the safety result of CHD Study is added to the ADVERSE REACTIONS section. The following statement is added to [redacted] (b) (4)

INDICATIONS and USAGE section is modified as follows: Synagis [redacted] (b) (4) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (≤35 weeks gestation age), *and children with hemodynamically significant CHD*. (See Clinical Studies [redacted] (b) (4)

Clinical Pharmacology and Pharmacokinetics Review of the Study Report
(MI-CP048, CHD Study)

Clinical Pharmacology

MI-CP048 was a randomized, double-blind, placebo-controlled, multicenter, multinational study, conducted during four consecutive RSV seasons, to determine the safety and efficacy of palivizumab in ≤2 year-old children with uncorrected, hemodynamically significant congenital heart disease (HSCHD), excluding uncomplicated patent ductus arteriosus, minor atrial septal defect, or minor ventricular septal defect. The primary objective was to compare the safety, tolerance, and efficacy of palivizumab to placebo when given monthly for the reduction of the incidence of RSV hospitalization among children with HSCHD.

A total of 1287 children were randomized (1:1) to receive either placebo or five monthly injections of 15 mg/kg of Synagis (palivizumab) during the RSV season in children with congenital heart disease. The study was conducted over four consecutive RSV seasons, but each child only participated during a single season. Subjects were stratified by cardiac lesion (cyanotic vs. acyanotic) and were followed for safety and efficacy for 150 days. Ninety-six percent (96%) of all subjects completed the study and 92% received all five monthly injections.

Blood collected prior to the first injection of study drug was evaluated for RSV neutralizing antibodies using a modification of the 60% plaque reduction test with complement. Data were summarized as those with RSV neutralizing titers < 1:200 and those with titers ≥1:200. RSV antigen testing was performed in the clinical laboratory at the site, using standard commercially available kits. Efficacy and safety results summarized by the sponsor are as follows:

Table 1. Efficacy Results Summarized by the Sponsor

	Placebo Group	Palivizumab Group	Reduction
RSV hospitalization*	63 of 648 (9.7%)	34 of 639 (5.3%)	45% (p=0.003)
Total days of RSV hospitalization			56% (p=0.003)
Total RSV days with increased supplemental oxygen			73% (p=0.014)

* Represent primary outcome. Data represent hospitalization outcomes as measured by days of RSV hospitalization per 100 randomized children.

According to the sponsor, the direction of the treatment effect was consistent over time, across geographic regions, across cardiac strata, and within subgroups of children defined by gender, age, weight, race, and presence of RSV neutralizing antibody at entry.

The incidence of adverse events (AEs) was similar in both groups. AEs with an incidence ≥1% higher (range 1.2%-3.2%) in the palivizumab group than the rate in the placebo group included fever, infection, injection site reactions, URI, conjunctivitis, arrhythmia, and cyanosis. No serious AEs related to palivizumab were reported and no drug discontinuation due to related AEs was reported.

The sponsor's conclusion is that monthly administration of Synagis (15 mg/kg) was safe, well tolerated and effective for prophylaxis of serious RSV disease in children ≤2 years

of age with congenital heart diseases, and resulted in a 45% reduction in the incidence of RSV hospitalization.

Pharmacokinetics

During clinical trial, blood samples for determination of trough serum palivizumab concentrations were collected from each child at three time points: 1) before the first injection of study drug (at baseline); 2) before the second scheduled injection, and 3) before the fifth scheduled injection. Serum palivizumab concentrations were also determined pre- and post- cardiac bypass in children undergoing open-heart surgery as a secondary endpoint. The ELISA used for measurement of serum palivizumab concentration was developed by the sponsor and is linear between 7.5 μg/ml and 100 μg/ml with the lower limit of quantitation (LLOQ) of 10 μg/ml. This assay has been validated. Results of palivizumab serum concentrations are summarized as follows:

Table 2. Serum Trough Concentrations of Palivizumab (Mean±SD with range)

	Palivizumab Group (n=639)	Placebo Group (n=648)
Pre-injection at Visit 2	n=456	n=477
Trough C (μg/ml)	55.5±19.5 (0-141.0)	0 (0-96.9)
Pre-injection at Visit 5	n=559	n=559
Trough C (μg/ml)	90.8±35.4 (0-211.0)	0 (0-46.3)

* A small number of children (2.6% in the palivizumab group and 0.7% in the placebo group) had results inconsistent with their treatment group assignment at a single time point, presumably due to sample processing errors or laboratory reporting errors.

Table 3. Serum Concentrations of Palivizumab for Patients Who Underwent Bypass (Mean±SD)

	Palivizumab Group (n=639)	Placebo Group (n=648)
Total # of bypass surgery	n=190	n=195
Pre bypass C (μg/ml)	98.0±51.6 (n=139)	0 (n=135)
Post bypass C (μg/ml)	41.4±33.1 (n=139)	0 (n=135)

Summary

- Mean trough serum palivizumab concentrations after the first and fourth palivizumab injections were 56±20 μg/ml and 91±35 μg/ml, respectively. These data are higher compared to the values reported in the previous studies (PDR) which were 37±21 μg/ml, and 72±50 μg/ml, respectively.

- Among 139 children receiving palivizumab who had cardio-pulmonary bypass and for whom paired serum samples were available, the mean serum palivizumab concentration was 98 μg/ml pre-cardiac bypass and declined to 41 μg/ml after bypass, a reduction of 58%.

Potential Effect of Covariates (Race, Gender, Age, Body Weight or Concomitant Medications) on Palivizumab Systemic Exposure

In response to a request by this reviewer, the sponsor conducted an analysis to assess the potential effect of demographic parameters and of concomitant medications on serum palivizumab concentrations.

Table 4. Gender Effect on Palivizumab Concentrations (μg/ml)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
Male	55.5±19.2 (N=257)	90.1±36.9 (N=313)
Female	55.5±19.9 (N=199)	91.6±33.4 (N=246)

Table 5. Age (Months, at Study Entry) Effect on Palivizumab Concentrations (μg/ml)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
≤Percentiles	50.5±17.1 (N=114)	90.5±38.2 (N=140)
>25-50 Percentiles	55.2±20.3 (N=115)	91.6±33.8 (N=134)
>50-75 Percentiles	60.7±21.7 (N=118)	95.7±37.8 (N=139)
>75 Percentiles	55.4±17.1 (N=109)	85.5±31.1 (N=146)

Table 6. Weight (kg, at Study Entry) Effect on Palivizumab Concentrations (μg/ml)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
≤Percentiles	49.0±18.5 (N=118)	85.0±34.2 (N=136)
>25-50 Percentiles	51.8±18.3 (N=115)	95.0±37.0 (N=141)
>50-75 Percentiles	62.9±19.5 (N=114)	89.5±37.5 (N=139)
>75 Percentiles	58.7±18.7 (N=109)	93.3±32.3 (N=143)

Table 7. Race Effect on Palivizumab Concentrations (μg/ml)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
Caucasian	57.1±19.0 (N=327)	94.9±34.1 (N=399)
Black	49.5±17.8 (N=38)	85.5±38.9 (N=40)
Hispanic	49.8±22.2 (N=48)	71.6±37.7 (N=69)
Asian	58.4±12.2 (N=9)	99.0±29.0 (N=13)
Other	53.3±20.8 (N=34)	84.7±31.5 (N=38)

Table 8. Concomitant Medications on Palivizumab Concentrations (μg/ml) (1)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
Analgesics		
No	57.9±16.5 (N=118)	97.2±35.1 (N=133)
Yes	54.4±20.4 (N=333)	88.8±35.4 (N=421)
Anesthetics/Muscle Relaxants		
No	58.2±17.8 (N=260)	96.9±33.4 (N=324)
Yes	51.6±21.1 (N=191)	82.2±36.7 (N=230)
Anti-Infectives		
No	60.78±20.5 (N=117)	97.4±36.3(N=142)
Yes	53.6±18.8 (N=334)	88.5±35.0 (N=412)
Anticoagulants/Coagulants		
No	58.4±20.1 (N=224)	98.0±35.7 (N=274)
Yes	52.4±18.4 (N=227)	83.7±33.9 (N=280)
Antihistamines		
Hispanic	55.7±19.7 (N=418)	91.8±35.6 (N=510)
Asian	51.7±16.0 (N=33)	79.3±32.1 (N=44)
Cardiac medications		
No	60.1±19.0 (N=98)	98.1±32.3 (N=120)
Yes	54.1±19.5 (N=353)	88.8±36.1 (N=434)
GI medications		
No	56.9±19.1 (N=289)	94.2±34.3 (N=350)
Yes	52.7±20.0 (N=162)	85.0±36.8 (N=204)

Table 8. Concomitant Medications on Palivizumab Concentrations (μg/ml) (2)

Sampling Time	Pre-Injection at Visit 2	Pre-Injection at Visit 5
Mineral supplements		
No	58.9±17.7 (N=255)	96.1±33.9 (N=320)
Yes	50.8±20.7 (N=196)	83.6±36.4 (N=234)
Respiratory medications		
No	56.2±19.6 (N=337)	95.2±35.3 (N=402)
Yes	53.2±19.2 (N=114)	79.1±33.3 (N=152)
Sedatives		
No	57.7±18.1 (N=277)	95.7±32.6 (N=338)
Yes	51.8±21.1 (N=174)	83.1±38.4 (N=216)

Summary

Within each demographic parameter, no clinically significant differences in palivizumab concentration were observed between subgroups. Also, within each category of medications, no clinically significant differences in palivizumab concentration were observed between subgroups.

In conclusion, the demographic parameters and the concomitant medications analyzed had no clinically significant effect on trough serum palivizumab concentrations. In all the subgroups analyzed, the mean serum palivizumab concentration was higher than the target concentration of 30 μg/ml.

Comment

The sponsor mentions that submission of this study fulfills all post-marketing commitments agreed to at the time of product approval.

Recommendation

The sponsor proposed addition of the labeling statement in the pharmacokinetics section is factually correct, therefore this modification can be granted.

The following statements are suggested by this reviewer to add to the labeling under CLINICAL PHARMARCOLOGY:

(b) (4)

[redacted]

Please convey this recommendation to the Medical Review Team.

Hong Zhao 5/8/03

Hong Zhao, Ph.D.
Clinical Pharmacology Reviewer

Martin D. Green 5/8/03

Martin David Green, Ph.D.
Branch Chief, Clinical Pharmacology and Toxicology

Appendix
The following information is from PDR:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 15, 2003

From: Robert Davis

Subject: Compliance Check Completed for STN 103770/5033 - Acceptable

The facilites involved with the manufacture of this product are:

MedImmune, Inc.

(b) (4)

(b) (4)

(b) (4)

Product: Palivizumab (Synagis)

STN: 103770/5033

Summary: This BLA supplement is an efficacy sBLA for an expanded indication that includes children with hemodynamically significant congenital heart disease. There are no manufacturing or facility changes associated with this supplement.

There are no ongoing or pending investigations or compliance actions with respect to the above facilities or its product. Therefore, the CDER Office of Compliance, Division of Manufacturing and Product Quality does not object to the approval of this supplement.

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 15, 2003

FROM: Dale Slavin, Ph.D.
Regulatory Project Manager
Division of Application Review and Policy, HFM-588
Office of Therapeutics Research and Review

TO: STN 103770/5033

SUBJECT: SBA Equivalent for

- Product: Palivizumab (Synagis®)
- Manufacturer: MedImmune, Inc.
- License Number: 1252

Indications and Usage

Synagis® is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant CHD.

Dosage Form, Route of Administration, and Recommended Dosage

- Sterile lyophilized product for reconstitution with SWFI.
- Provided in a single use vial of 50 or 100 mg.
- Each single-use vial contains 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL solution.
- Palivizumab contains no preservatives
- Palivizumab is to be delivered intramuscularly (IM) at a dose of 15 mg/kg

Basis for Approval
The following reviews, filed in the CBER correspondence section of the license file for STN 103770/5033, comprise the SBA equivalent for this supplement:

Discipline	Reviewer Name	Date
Clinical/ Statistical	Linda Forsyth M.D., Boguang Zhen, Ph.D.	9-15-03
Clinical Pharmacology	Hong Zhao, Ph.D.	5-8-03; 9-8-03
Bioresearch Monitoring	Lloyd Johnson, Pharm.D.	9-17-03

LICENSING ACTION RECOMMENDATION

Applicant: MedImmune **STN:** 103770/5033

Product:

Palivizumab (Synagis)

Indication / manufacturer's change:

To expand the indication to include children with hemodynamically significant congenital heart disease.

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ■ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

☐ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

■ BiMo inspections completed ■ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ☐ Categorical Exclusion

■ Review of labeling Date completed 9-15-03 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

~~■ CBER Lot release not required~~

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Linda Forsyth
Review Committee Chairperson: Linda M. Forsyth Date: 9-15-03

Product Office's Responsible Division Director(s)*:

_____ Date: _____

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

☐ Compliance status checked ☒ Acceptable ☐ Hold Date: 9-15-03

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: 9-15-03

Responsible Division Director _____ FOR R.K. Date: 9/15/03
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (04/2003)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: September 11, 2003

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Representatives of MedImmune regarding FDA revisions to PI sent MedImmune 9-9-03

To: BLA STN: 103770/5033

Drs. Walton, Siegel, Forsyth, Marzella Slavin and Zhao called MedImmune as MedImmune had requested to discuss the PK/PD data and FDA suggested revisions to the PI (FDA sent to MedImmune on 9-9-03). Julia confirmed that MedImmune agrees to the FDA proposed language and changes. The Information presented in the PI is from the Impact trial data. (b) (4)

Regarding the delay of the dose of Synagis until a later time point post surgery. MedImmune stated that they did not feel this was medically appropriate as the highest risk of contracting RSV was post surgery. Thus it would not be in the infants' best interest to delay the Synagis dose. FDA was concerned about the drop in serum levels of drug post surgery, but was uncertain of the clinical significance, however if delaying a dose is problematic in medical management of the patient and delaying the dose until post surgery and possibly maintaining a higher level of Synagis would present a risk then we do not feel strongly that the physician should wait to dose the patient.

Regarding the discussion of Table one MedImmune was told that they needed to provide some understanding that these data don't support any expectation. They need to be very clear that there is no basis to expect any change in severity. MedImmune agreed to revise the PI accordingly.

Regarding the AEs we have concern with how CHD patients are characterized in their AEs. E.g., a CHD patient that is getting drug and receives another catheterization while on study. MedImmune stated that heart malformations are coded fundamentally and then the treatments for that malformation are coded as variations on medical care not new AE findings. FDA requested that MedImmune retabulate data as per trial that each AE comes from and identify those AEs that are anomalously left out or highlighted.

(b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

In a follow-up phone call we requested that they verify that the pooled numbers for AEs were actually pooled and that they are correct. We also requested that MedImmune ensure that the written and tabular portions of the PI are in agreement.

Attached are the MedImmune requested discussion topics and the FDA revised PI sent MI on 9-9-04

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

MedImmune, Inc.

From: Julia Goldstein, Regulatory Affairs, MedImmune, Inc

To: Dale Slavin, DARP, FDA

Dear Dr Slavin,

MedImmune has reviewed the revised draft of the Synagis® PI received from the Agency on September 9, 2003. We agree with all changes suggested by the reviewers with the exceptions noted below. We wish to discuss these with the review team during the teleconference today. Please call in to the following number at 11:00am.

(b) (4)

FDA recommendations for discussion are shown in italics. MedImmune additions are shown in normal font. The page referenced correlates with the PI received on September 9.

Comment 1 – Page 2

"The clinical significance of this reduction is unknown"

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Slavin, Dale

From: Goldstein, Julia [GoldsteinJ@MedImmune.com]
Sent: Friday, September 12, 2003 1:38 PM
To: slavind@cber.fda.gov
Subject: Fax and Attendees

Meeting participants
1. Ed Connor (Clinical)
2. Dave Carlin (stats)
3. Peter Patriarca (RA)
4. Genny Losonsky (Clinical)
5. Julia Goldstein (RA)

The fax is 301-527-4216... My"card" is for your records.

Thanks for all the help

BLA/NDA/PMA
Review Committee Assignment Memorandum

❑ Initial Assignment
X Change

STN: 103770/5033

Applicant: MedImmune, Inc.
Product: Palivizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Dale Slavin	Reg. Coordinator	Admin/Regulatory	W. Aaronson	11-25-02
	Reviewer	Admin/Regulatory		
Linda Forsyth	Reviewer	Clinical	Jeffrey Siegel	11-25-02
		Product		
		Product		
Louis Marzella		Clinical – Team leader	Jeffrey Siegel	6-1-03
		Clinical		
Hong Zhao	Reviewer	Clinical Pharmacology	Dave Green	11-25-02
		Pharm/Tox		
Boguang Zhen	Reviewer	Biostatistics	C. Anello	7-3-03
		BiMo		
		Epidemiology		
		Facility		
J. Lloyd Johnson	Reviewer	Inspector	Robert Leedham	6-24-03
		Labeling		
		Other		

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
William Tauber	Reviewer/Chair	Clinical	Weiss/Siegel	11-25-02
Yuan Who Chen	Reviewer	Biostatistics	G. Gupta/Anello	7-3-03jo
Estella Z. Jones	Reviewer	Inspector	Robert Leedham	6-24-03

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Dale Slavin _____ 9-15-03
Name Printed Signature Date

Memo entered in RMS by: _____ Date: _____ QC by: CJO Date: 9-22-03

*M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 11, 2003

TO: Dale C. Slavin, Ph.D., Regulatory Project Manager
Linda M. Forsyth, M.D., Medical Officer, Chair & Clinical Reviewer
Louis Marzella, M.D., Medical Team Leader, Clinical Reviewer
Jeffrey Siegel, M.D., Branch Chief, Clinical Reviewer
Immunology and Infectious Disease Branch
Division of Clinical Trials Design And Analysis, HFM-582

THROUGH: Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch 1 (HFD-46)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch 1 (HFD-46)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: STN 103770/5033

APPLICANT: MedImmune, Inc.

DRUG: Synalgis (palivizumab)

CHEMICAL CLASSIFICATION: Type 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Prophylaxis of Respiratory Syncytial Virus (RSV) in Children with Congenital Heart Disease (CHD)

CONSULTATION REQUEST DATE: April 29, 2003

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: September 11, 2003

ACTION GOAL DATE: September 15, 2003

I. BACKGROUND

Palivizumab (Lyophilized MEDI-493, Humanized Respiratory Syncytial Virus Monoclonal Antibody) is an F-protein-specific humanized monoclonal antibody (IgG1) that neutralizes a broad range of RSV isolates by binding to a protein on RSV. This product is currently licensed for the prevention of serious lower respiratory tract disease cause by RSV in high risk pediatric patients. MedImmune, Inc., is now seeking an expanded indication for Prophylaxis of Respiratory Syncytial Virus (RSV) in Children with Congenital Heart Disease (CHD). Data from a Phase III, randomized, double-blind, placebo-controlled, multi-center pivotal study (Protocol MI-CP048), was submitted in support of the new indication.

II. RESULTS (by site):

NAME (Site #)	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR RECED.	CLASSN.
Cody H. Meissner, M.D. (001)	Boston, MA	USA	MI-CPO48	May 18-26, 2003	July 31, 2003	VAI
Frank Fai Ing, M.D. (022)	San Diego, CA	USA	MI-CPO48	May 3-12, 2003	July 24, 2003	VAI
Timothy F. Feltes, M.D. & Antonio R. Motts, M.D. (014)	Houston, TX	USA	MI-CPO48	July 18-23, 2003	August 14, 2003 Draft	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection/Report not completed

Study Protocol:

MI-CP048: A Study of the Safety, Tolerance, and Efficacy of Palivizumab (MEDI-493, Synalgis®) for Prophylaxis of Respiratory Syncytial Virus in Children with Congenital Heart Disease

A Phase III randomized, double-blind, placebo-controlled, multi-center, multinational trial was conducted to determine the safety and efficacy of palivizumab in preventing serious RSV disease in children with CHD. A total of 1287 children were randomized, 639 to Palivizumab and 648 to placebo, over three to four RSV seasons. Each child was only to participate during a single RSV season. Eligible children were under 24 months of age at randomization and had a congenital heart defect (other than uncomplicated patent ductus arteriosus, minor atrial septal defect, or minor ventricular septal defect) that was not definitively corrected at the time of randomization. Randomization (1:1) was blocked by site and stratified according to whether the patient had anatomical cyanotic CHD. All children randomized into the study were to be followed for adverse events and hospitalizations through 150 days after randomization, regardless of the number of study drug injections received. Children received injections of study drug, either 15-mg/kg palivizumab or an equivalent volume of placebo, every 30 days for a total of five injections. A final follow-up visit was to occur 30 days after the fifth injection (Study Day 150). Children were to be closely monitored by observation for 30 minutes after each injection of study drug. Regular monthly evaluations were to consist of a medical history and physical examination.

The trial was conducted at 76 investigative sites: 47 sites in the US, 6 in Canada, and 23 in Europe (4 in France, 4 in Germany, 6 in Poland, 3 in Sweden, and 6 in the UK).

The first subject was randomized on November 2, 1998 and the last study visit was completed May 2, 2002.

The primary objective was to compare the safety, tolerance, and efficacy of palivizumab to placebo when given monthly for the reduction of the incidence of RSV hospitalization among children with hemodynamically significant congenital heart disease.

The secondary objectives were to:

- Determine the effect of monthly palivizumab prophylaxis compared to placebo on RSV hospitalization outcomes and disease severity (as measured by total days of RSV hospitalization per 100 randomized children, the total RSV hospital days with increased oxygen requirement per 100 randomized children, the incidence and total days of RSV-associated intensive care per 100 randomized children, and the incidence and total days of RSV-associated mechanical ventilation per 100 randomized children);
- Describe the effect of cardiac bypass on serum palivizumab concentrations;
- Determine palivizumab trough concentration before the second and fifth doses.

Basis for site selection: The following sites were selected for inspection because of their high enrollment, geographic location and response rates.

(1) Cody H. Meissner, M.D. (Site 001) (Number enrolled: 45 subjects) (FACTS # 416980)
Pediatric Infectious Disease
New England Medical Center, #321
750 Washington Street
Boston, MA 02111

Inspection dates: May 18-26, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected:

50 subjects were screened for the study; 45 were enrolled. The field investigator examined study records for 15 of the 45 subjects enrolled, and compared case report forms to source documents for the 15 subjects.

b. Limitations of inspection: None

c. General observations/commentary

CRFs accurately reflected data recorded in source documents. All 15 subjects' records inspected were found to have the condition required for the study and met inclusion/exclusion criteria.

AEs and SAEs were reported accurately and in a timely manner. Concomitant meds were spot checked and found to be accurate.

Informed consent for all subjects enrolled were reviewed and found to be in compliance.

The inspection revealed that results of Palivizumab concentrations & RSV neutralizing AB titers were not found in the subjects's records for study visit (Day 0) (FDA 483 Item 1). This observation is not valid since the laboratory results for serum concentration and antibody titers are sent and analyzed at a central laboratory and the laboratory results are sent to the sponsor not the investigators. Therefore, the laboratory raw data would reside at the central laboratory location not at the study sites.

Drug storage procedure and temperature monitoring records for Pavlizumab were found complete and followed protocol requirements. Drug accountability records for the four-year study period were found to be generally accurate with the exception of Year 1 (1998 – 1999); record review revealed that 8 vials of the study drug could not be accounted (FDA 483 Item 2).

Dr. Meissner responded to this 483 item in a letter dated July 30, 2003 in which he explained that the 8 vials of unused drug were returned to MedImmune in November 1999 but the study pharmacist inadvertently did not retain a copy of the study drug return documentation. Dr. Meissner provided assurances that additional staff training on procedures will be implemented as part of their corrective action to prevent repetition of this observation in future studies. In response to FDA 483-Item 1, Dr. Meissner also re-iterated in his response letter that laboratory raw data or source documents would not be found at the clinical investigators site for the reasons explained above.

No other deviation was noted.

Recommendation: Data from this site are acceptable.

(2) Frank Fai Ing M.D. (Site 022) (Number enrolled: 39 subjects) (FACTS # 416999)

Children's Hospital and Health Center
3020 Children's Way/MC 5004
San Diego, CA 92123

Inspection Dates: May 3-12, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected:

39 subjects were enrolled, 36 subjects completed the study. Complete study records for 26 of the 39 subjects enrolled were audited. Case report forms were compared with source documents for the 26 subjects.

b. Limitations of inspection: None.

c. General observations/commentary

In general, the source documents were organized, complete, and legible. CRFs accurately reflected data recorded in source documents. All 26 subjects met study entry criteria, subject records included observation data and information on subject conditions throughout the duration of the study.

Concomitant medications and AEs were reported accurately. All informed consents were reviewed and were found to be complete.

A two-item FDA 483 was issued covering protocol deviations and drug accountability. The inspectional observations are considered minor with no significant impact on safety and efficacy data.

Recommendation: Data from this site are acceptable.

(3) Timothy F. Feltes, M.D./Antonio Mott, M.D. (Site 014) (Number enrolled: 38 subjects) (FACTS #417008)

c/o Texas Children's Hospital
6621 Fannin Street
Houston, TX 77030

Inspection Dates: July 18-23, 2003

Methodology: Inspection assignments were issued to the field office.

a. What was inspected:

60 subjects were screened, 38 subjects were randomized, 33 subjects completed the study. Complete study records for 12 of the 38 subjects enrolled were audited. Case report forms were compared with source documents for the 12 subjects.

b. Limitations of inspection: Dr. Timothy F. Feltes, original principal investigator for this study site was not available during the inspection. Dr. Feltes transferred to another university and has designated Dr. Antonio Mott and Dr. Timothy Bricker, sub-investigators, as responsible for the study records. Dr. Feltes performed the screening, provided and collected patient consent forms, administered the test article, performed follow-up exams and reviewed the case report forms prior to his departure for this study.

c. General observations/commentary

Source documents case report forms, medical charts and sponsor data listings were compared. Adverse events, concomitant medication and laboratory test records were reviewed and compared. Review of records revealed no major objectionable conditions.

No FDA 483 was issued. (EIR is in the process of being completed, inspection results obtain by phone contact and e-mail correspondence with FDA field investigator).

Recommendation: Data from site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the sites inspected, there was sufficient documentation to assure that all study subjects audited did exist, fulfilled eligibility criteria, received assigned study medication, and adequately reported adverse events. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

There were minor issues related to protocol deviations and drug accountability documentation at Dr. Ing's site (022) and a minor drug accountability record keeping issue at Dr. Meissner site (001). The inspection of Dr. Feltes/Dr. Mott study site revealed no significant observations.

[Note: The review and evaluation of Dr. Feltes/Dr. Mott's audit was based on a draft EIR and preliminary input from the field investigator via electronic mail and telecommunication. Should the official EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the BLA review committee and the review division.]

The data submitted in support of this BLA appear acceptable.

Follow-up action: none

J. Lloyd Johnson, Pharm.D.,
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Khin Maung U, M.D.
Branch Chief, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

DISTRIBUTION:
HFM-99: BLA: STN 103770/5033
HFM-99: BB-IND 5862
HFM-582: MO (Forsyth, Linda M., Chair, STN 103770/5033)
HFM-588: PM (Slavin, Dale C.)
HFD-46/Johnson
HFD-45/Division File
HFD-45/Reading File
HFD-45/Program Management Staff (electronic copy)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: September 9, 2003

From: Dale Slavin, Ph.D., OTRR/DRMP DS

Subject: Submitted revisions to MedImmune for package insert

To: BLA STN: 103770/5033

FDA submitted the following revisions to MedImmune regarding the CHD study and the proposed language within the package insert.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 24, 2003

From: Dale Slavin, Ph.D. OTRR/DARP

Subject: **Internal Meeting** regarding FDA/BLS 103770/5033 (MedImmune, Palivizumab) Midcycle for Clinical Efficacy Supplement regarding PMC #2 To design and conduct a safety study in pediatric congenital heart disease patients (CHD study MI-CP048)

To: **FDA Review Committee**
Linda Forsyth, M.D.
Lloyd Johnson, Pharm.D.
Louis Marzella, M.D.
Jeffrey Siegel, M.D.
Dale Slavin Ph.D.
Marc Walton, M.D., Ph.D.
Hong Zhao, Ph.D.
Boguang Zhen, Ph.D.

Purpose: To discuss all outstanding issues regarding the supplement.
To initiate discussion, and propose a response to the draft labeling changes.
To determine if the supplement can move towards approval.

Regulatory – Dale Slavin

MedImmune has submitted all the required paperwork
a. Financial disclosure
b. Payment
c. Debarment statement

Final Action Due – September 15, 2003

Biological Monitoring – Estella Jones, Replaced by Lloyd Johnson

1. Inspection requests were sent July 1, 2003, for sites in Boston, Houston, and Los Angeles.
   - Two sites have been audited:
     - Boston, Dr. Cody Meissner (45 subjects);
       - No 483 for Dr. C. Meissner.

- LA, Dr. Frank Fai Ing (39 subjects).
  - 483 for Dr. F.F. Ing, no data discrepancy or integrity issues, some protocol deviations.

- Houston, Dr. Timothy F. Feltes (38 subjects) is scheduled for the last week of July.

2. Do not have inspection reports as of yet on any of the sites.

Statistical – Richard Chen, Replaced by Boguang Zhen

1. Efficacy analysis – acceptable

2. Sensitivity analysis – acceptable

3. RSV Hospitalization - concerns with how determine hospitalization
   - Defining criteria for hospitalization
   - Defining events

Clinical Pharmacology – Hong Zhao

1. No issues with study

2. Suggested additional statement for the PI

Clinical – Linda Forsyth, Louis Marzella, Jeffrey Siegel and Marc Walton

1. No major issues were found with submission

2. Study Design

3. Baseline demographics

4. Primary endpoint
   - Incidence of RSV hospitalization by stratum

5. Secondary endpoint
   - Consistent with primary endpoint
     - Question of less severe disease
     - Question of whether this adds anything to label

6. Safety - acceptable

7. Conclusions regarding study – all appears acceptable

8. Outstanding issues
Minor issues on wording in the PI. Will request that changes be made

Clinical and Stat review will be submitted as a joint review

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Date: 7/24/2003

From: J. Lloyd Johnson, Pharm.D.
Division of Scientific Investigations
Good Clinical Practice Branch II
OMP, HFD-45

Bioresearch Monitoring Inspections Update

SPONSOR	MedImmune, Inc. 35 West Watkins Mill Rd Gaithersburg, MD 20878
BLA REF	BLS 103770/5033 Final Action Due – September 15, 2003
PRODUCT	Palivizumab (Humanized RSV Mab) (Synalgis®)
INDICATION	Prophylaxis of RSV in children with Congenital Heart Disease
PROTOCOL #	MI-CP048
IND REF	BB-IND 5862

- CBER/DIS Inspection Assignment Memo and Inspection Document Package for clinical data verification issued to 3 FDA Field Offices

- 3 study sites listed on page 2 are scheduled to be audited under the Bioreasearch Monitoring Program designed to verify reliability of clinical data

- Data audits will cover clinical study records for Study Protocol MI-CPO48

- Inspections of 2 study sites completed. Remaining site (Dr. Feltes) scheduled for end of July:
  Dr. Meissner – No FDA 483 issued
  Dr. Fai Ing – Received an FDA 483 – observations do not appear to be serious (possible clinical protocol deviations in 4 study subjects related to errors in the accuracy of dosing) - no data integrity or data discrepancy issues or major problems/observations requiring invalidation of data
- All inspection results should be in before the BLA action due date
- BIMO Inspection Summary/Recommendation Memo – summarizing all violations and inspectional findings will be prepared following complete review of all 3 EIRs, evidence exhibits, and all documentation
- Any compliance action letters will issue to clinical investigators or sponsor if warranted

Investigators Scheduled to be audited:

(NWE-DO)
Cody H. Meissner, M.D.
Pediatric Infectious Disease
New England Medical Center, #321
750 Washington Street
Boston, MA 02111
(617) 636-5227

Site 001
#Subjects = 45

(LOS-DO)
Frank Fai Ing, M.D.
Children's Hospital and Health Center
3020 Children's Way/MC 5004
San Diego, CA 92123
(619) 576-5855

Site 022
Subjects = 39

(DAL-DO)
Timothy F. Feltes, M.D.*
c/o Texas Children's Hospital
6621 Fannin Street
Houston, TX 77030
(832) 826-5600

Site 014
#Subjects = 38

103770/5033

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE APR 29 2003

FROM Estella Jones, D.V.M., Bioresearch Monitoring Branch, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Telephone: 301-827-6335 FAX: 301-827-6748

CP: 7348.811
PAC: 41811
Priority: High
Due Date: 60 Days

PLEASE NOTE: This BLA is being reviewed under the managed review time frames established by the Prescription Drug User Fee Act (PDUFA). Please complete the inspection by July 1, 2003. Please FAX the Form FDA 483, if issued, to the number listed above.

TO Director, Investigations Branch
New England District Office, HFR-NE 250 FACTS # 416980
~~Dallas District Office, HFR-SW150 FACTS # 417008~~
Ron Koller, BIMO Coordinator, Los Angeles District Office
HFR-PA2565 FACTS # 416999

General Instructions

We request that inspections of the following clinical investigators be performed in accordance with CP 7348.811:

CLINICAL INVESTIGATORS

(NWE-DO)
Cody H. Meissner, M.D. Site 001
Pediatric Infectious Disease #Subjects = 45
New England Medical Center, #321
750 Washington Street
Boston, MA 02111
(617) 636-5227

(LOS-DO)
Frank Fai Ing, M.D. Site 022
Children's Hospital and Health Center # Subjects = 39
3020 Children's Way/MC 5004
San Diego, CA 92123
(619) 576-5855

(DAL-DO)
Timothy F. Feltes, M.D.*
c/o Texas Children's Hospital
6621 Fannin Street
Houston, TX 77030
(832) 826-5600

Site 014
#Subjects = 38

*Note: Dr. Timothy Felts transferred to Children's Hospital in Columbus, Ohio, during the study. We suggest you contact the research administration office or IRB to schedule review of the records at Texas Children's Hospital.

PROTOCOL	A Study of the Safety, Tolerance, and Efficacy of Palivizumab (MEDI-493, Synagis®) for Prophylaxis of Respiratory Syncytial Virus in Children with Congenital Heart Disease
PROTOCOL #	MI-CP048
SPONSOR	MedImmune, Inc.
IND REF	BB-IND 5862
STN	103770/5033.0
PRODUCT:	Palivizumab (Lyophilized MEDI-493, Humanized Respiratory Syncytial Virus Monoclonal Antibody)
TRADE NAME	Synagis®

Background

Respiratory Syncytial Virus (RSV) is the leading cause of pneumonia and bronchiolitis in infants. For most otherwise healthy children, RSV usually amounts to little more than a cold. Outbreaks typically occur in the Northern Hemisphere November through April and are the most common cause of respiratory infection in infants and children worldwide. RSV can be a devastating and deadly disease in high-risk populations, such as children with prematurity, bronchopulmonary dysplasia (BPD), and congenital heart disease (CHD). In the U.S. alone, more than 90,000 children are hospitalized due to RSV and 4,500 die from the disease annually.

The FDA first licensed palivizumab in 1998 for the prevention of serious lower respiratory tract disease caused by RSV in high-risk pediatric patients. Safety and

efficacy were established in infants with BPD and in premature infants. Palivizumab is a F-protein-specific humanized monoclonal antibody (IgG1) that neutralizes a broad range of RSV isolates by binding to a protein on RSV. Palivizumab proved to be 50 to 100 times more potent than the previously available RSV hyperimmune globulin that required intravenous administration, allowing a smaller volume to be administered. Palivizumab is provided in 5 mL vials as a sterile, lyophilized product to be reconstituted in 1 mL sterile water for intramuscular injection (USP) to yield a final concentration of 100 mg/mL. The recommended therapeutic dose is 15-mg/kg body weight.

Palivizumab had not been previously studied in children with CHD. Children with CHD are at particularly increased risk for severe RSV disease, with significantly longer hospitalizations and increased oxygen requirements relative to children without CHD. Children with CHD and pulmonary hypertension also appeared to have the highest risk for mortality associated with RSV infection.

Protocol MI-CP048

A Phase III randomized, double-blind, placebo-controlled, multi-center, multinational trial was conducted to determine the safety and efficacy of palivizumab in preventing serious RSV disease in children with CHD. A total of 1287 children were randomized, 639 to palivizumab and 648 to placebo, over three to four RSV seasons. Each child was only to participate during a single RSV season. Eligible children were under 24 months of age at randomization and had a congenital heart defect (other than uncomplicated patent ductus arteriosus, minor atrial septal defect, or minor ventricular septal defect) that was not definitively corrected at the time of randomization. Randomization (1:1) was blocked by site and stratified according to whether the patient had anatomical cyanotic CHD. All children randomized into the study were to be followed for adverse events and hospitalizations through 150 days after randomization, regardless of the number of study drug injections received. Children received injections of study drug, either 15-mg/kg palivizumab or an equivalent volume of placebo, every 30 days for a total of five injections. A final follow-up visit was to occur 30 days after the fifth injection (Study Day 150). Children were to be closely monitored by observation for 30 minutes after each injection of study drug. Regular monthly evaluations were to consist of a medical history and physical examination. A high proportion of children on the study (93.0% palivizumab and 91.8% placebo) received all 5 monthly doses of the study drug.

The trial was conducted at 76 investigative sites: 47 sites in the US, 6 in Canada, and 23 in Europe (4 in France, 4 in Germany, 6 in Poland, 3 in Sweden, and 6 in the UK). The first subject was randomized on November 2, 1998 and the last study visit was completed May 2, 2002.

Objectives

Primary:

The primary objective was to compare the safety, tolerance, and efficacy of palivizumab to placebo when given monthly for the reduction of the incidence of RSV hospitalization among children with hemodynamically significant congenital heart disease.

Secondary:

The secondary objectives were to:

- Determine the effect of monthly palivizumab prophylaxis compared to placebo on RSV hospitalization outcomes and disease severity (as measured by total days of RSV hospitalization per 100 randomized children, the total RSV hospital days with increased oxygen requirement per 100 randomized children, the incidence and total days of RSV-associated intensive care per 100 randomized children, and the incidence and total days of RSV-associated mechanical ventilation per 100 randomized children);
- Describe the effect of cardiac bypass on serum palivizumab concentrations;
- Determine palivizumab trough concentration before the second and fifth doses.

A total of 48 children died during the study; 21 (3.3%) in the palivizumab group and 27 (4.2%) in the placebo group. The sponsor did not attribute any deaths to the study drug. Deaths associated with RSV infection occurred in 2 subjects in the palivizumab group and 4 subjects in the placebo group. The sponsor concluded that palivizumab at its indicated dose of 15mg/kg was safe, well tolerated and effective for prophylaxis of serious RSV illness in infants and children under 2 years of age with congenital heart disease with a 45% reduction in the incidence of RSV hospitalization.

Request

Please conduct an inspection according to the compliance program. The inspection should focus on the safety, tolerance and efficacy highlighted in the enclosed tables from the BLA submitted by the sponsor. We request that you compare records and case reports forms with the attached data from the BLA. **Please provide documentation of any discrepancies found.**

General

1. Please obtain a copy of the following:

    a. A copy of the signed 1572 and a copy of the clinical investigator's CV.

    b. A copy of the IRB approval for the study and significant reports to the IRB.

c. A representative copy of signed consent form(s) used at the site.

d. A copy of the protocol and any amendments used at the site if they are different from the version in the attachments.

e. A list of all clinical trials conducted by the clinical investigator(s). Please include the title of the study, the protocol number, and the associated IND/IDE or BLA/NDA number.

2. Please determine the frequency of sponsor monitoring conducted at the site during the study. Describe how the sponsor monitored the study, and how monitoring activities were documented.

3. Did the subjects meet the eligibility criteria and none of the exclusion criteria as outlined in Section 3.1 of the attached protocol (Attachment A and Attachment E)?

4. Did the clinical investigator follow the protocol? Refer to Attachment B for a listing of study subjects at each site and Attachment C for a listing of protocol deviations. If additional deviations are found, please provide documentation.

5. Please check **all** serious adverse events and deaths listed by the sponsor to the study subject records and note any discrepancies in the data (Attachment D).

6. Adverse events were to be monitored throughout the course of the study (including 30 minutes post injection) through clinical examinations and blood tests. Please spot check the reporting of adverse events, vital signs before and after administration of study drug, site of injection reactions and discontinuation of study drug (Attachment F).

7. Were adverse experiences, including deaths, reported in a timely manner, as required by Section 4.2.2 and 4.2.3 of the protocol (Attachment A)?

8. Please spot check serum palivizumab concentrations (prior to the second and fifth injections) and RSV neutralizing antibody titers submitted by the sponsor with the subject's records and document any discrepancies (Attachment G).

9. Please check all analysis for pre- and post-surgery levels of serum palivizumab obtained for patients undergoing cardiopulmonary bypass, if the sample was available (Attachment H).

10. Please spot check the randomized reporting of total days of hospitalization due to RSV, to include oxygen requirements, RSV-associated intensive care and RSV-associated mechanical ventilation against the original records (Attachment I).

11. Please spot check the dosing schedule established for study subjects. Determine how visits were rescheduled, if necessary, to keep within the established dosing interval window. How was an alternate injection schedule established and recorded (Attachment A, Section 3.3.3)?

12. Please check the drug accountability log to verify accuracy of records for the receipt and disposition of the test article. Determine where test articles were stored and if they were maintained under the appropriate storage conditions, as described in Section 3.3.1 of Attachment A.

13. Please spot check the use of concomitant medications against the source documents for accuracy (Attachment J). These are lengthy because the subjects were quite ill.

Please contact me at the phone number below prior to the initiation of the inspection for updated information and any questions concerning this assignment.

Please send the establishment inspection report and exhibits by first class U.S. mail or overnight carrier to:

Estella Jones, D.V.M.
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 400S
Rockville, MD 20852-1448
Tel. 301-827-6335

Estella Jones

Estella Jones, D.V.M.
Senior Regulatory Officer

Attachments:

Attachment A – Study Protocol, version 5.0
Attachment B – Listing of Study Subjects per Site
Attachment C – Protocol Deviations
Attachment D – Listing of Deaths and Serious Adverse Events
Attachment E – Listing of Inclusion/Exclusion Criteria
Attachment F – Listing of Scheduled Injection Visits Assessments
Attachment G – Listing of Serum Palivizumab Concentrations and RSV Neutralizing Antibody Titers
Attachment H – Listing of Cardiac Surgery/Interventional Catheterizations
Attachment I – Listing of RSV Hospitalizations and RSV Hospitalization Tracking
Attachment J – Listing of Concomitant Medications

Cc:

Hard Copy

HFM-99	IND # 5862
HFM-664	Access/CHRON
HFM-664	EZJ
HFM-582	Forsyth, Linda M., Chair, STN 103770/5033
HFM-588	Clevin, Dale C.
HFM-650	Cole
HFR-NE200	Gail T. Costello, Director
HFR-NE250	Michael R. Kravchuk, Dir., Invest. Branch
HRF-NE250	Ellen Madigan, Bimo Monitor with Attachments
HFR-SW100	Michael A. Chappell, Director
HFR-SW150	H. Tyler Thornburg, Dir. Invest. Branch
HFR-SW1540	Joel Martinez, Bimo Monitor with Attachments
HFR-PA200	Alonza E. Cruse, District Director
HFR-PA250	Acting Director, Domestic Invest.
HFR-PA2565	Ron Koller, Bimo Monitor with Attachments

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 23, 2003

From: Dale C. Slavin, Regulatory Project Manager, OTRR/DARP

Subject: Filing Meeting for MedImmune Palivizumab STN 103770/5033
A study evaluating Palivizumab in pediatric patients with congenital heart disease.

To: Attendees

Meeting Date: January 7, 2003

Yuan Who Chen	Biostats
Linda Forsyth	Clinical
Estella Z. Jones	Clinical Site Inspector
Dale Slavin	RPM
Hong Zhao	Clinical Pk/Pd

This was the internal filing meeting for the 10 month PAS for Palivizumab. No major deficiencies were cited. The filing review memo were said to be filled out and were awaiting Branch Chief and Division Director sign-off. Hong Zhao recommends that MedImmune perform additional analyses of the data to determine the effect(s), that each of the following gender, age, race or concomitant medication has upon Palivizumab exposure in congenital heart disease patients. The issue of data reanalysis could be addressed in the 74 day letter. It was agreed upon that MedImmune supplement 103770/5033 is filable.

Slavin (5)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 103770/6033 Product: Palivizumab Applicant: MedImmune

Final Review Designation (circle one): (Standard) Priority

~~Submission Format (circle all that apply): Paper Electronic (Combination)~~

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 1-7-03 Committee Recommendation (circle one): File RTF

RPM: [signature] / 1-23-03
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ✓ Part A – RPM
  - ___ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ✓ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): Hong Zhao
  - ✓ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Hong Zhao Linda Forsyth Chen Ynan Uho
- ☒ Memo of Filing Meeting

STN 103770/5033 Product Palivizumab

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	(Y) N	
Form 356h completed	(Y) N	
▫ including list of all establishment sites and their registration numbers	(Y) N	
▫ If foreign applicant, US Agent signature.	Y N	N/A
Comprehensive Table of Contents	(Y) N	
Debarment Certification with correct wording (see * below)	Y N	Send as amendment called 1-24-03
User Fee Cover Sheet	(Y) N	Sent as amendmentt
User Fee payment received	(Y) N	"
Financial certification &/or disclosure information	Y N	Sent as amendment
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Pediatric rule: study, waiver, or deferral	Y N	N/A
Labeling:	(Y) N	
▫ PI –non-annotated	(Y) N	
▫ PI –annotated	(Y) N	
▫ PI (electronic)	(Y) N	
▫ Medication Guide	Y (N)	
▫ Patient Insert	Y (N)	
▫ package and container	Y (N)	
▫ diluent	Y (N)	
▫ other components	Y (N)	
▫ established name (e.g. USAN)	(Y) N	
▫ proprietary name (for review)	Y (N)	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	(Y) N	
▫ legible	(Y) N	
▫ English (or translated into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	Y N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	
▫ summary reports reference the location of individual data and records	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	Not Applicable
if CMC supplement:		
☐ description and results of studies performed to evaluate the change	Y N	Not Applicable
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☐ changes in labeling clearly highlighted	(Y) N	
☐ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	Y N	Not Applicable

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? No

Does this submission relate to an outstanding PMC? Yes, Congenital Heart Disease #2

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one): (File) RTF

RPM Signature: [signature] Branch Chief concurrence: [signature]

Zhao (D)

STN 103770/5033 Product Palivizumab

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Non-clinical overview [2.4]	(Y)	N	
Non-clinical summary [2.6]	(Y)	N	
▫ Pharmacology	(Y)	N	
▫ Pharmacokinetics	(Y)	N	
▫ Toxicology	Y	N	

CTD Module 4 Contents	Present?		If not, justification, action & status
Module Table of Contents [4.1]	(Y)	N	
Study Reports and related info. [4.2]	(Y)	N	
▫ Pharmacology	(Y)	N	
▫ Pharmacokinetics	(Y)	N	
▫ Toxicology	Y	N	
Literature references and copies [4.3]	Y	N	

Examples of Filing Issues	Yes?		If not, justification, action & status?
content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
▫ legible	(Y)	N	
▫ English (or translated into English)	(Y)	N	
▫ compatible file formats	(Y)	N	
▫ navigable hyper-links	(Y)	N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y)	N	
▫ summary reports reference the location of individual data and records	(Y)	N	
▫ protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	(Y)	N	
▫ all electronic submission components usable	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y)	N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	(Y)	N	

Examples of Filing Issues	Yes?	If not, justification, action & status
animal reproduction studies included, if the biological product is to be administered to people with reproductive potential, unless an explanation of why such studies are not applicable	Y N	
includes carcinogenicity and/or reproductive and developmental toxicology studies deemed necessary by well established agency interpretation or communication during the IND review process	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Comment to the sponsor (not a filing issue):

Please analyze serum palivizumab concentration data to see whether race, gender, age, body weight or concomitant medication has any effect on palivizumab systemic exposure. The sponsor should propose an analysis plan (what data and what method(s) ~~are going to~~ will be used for this analysis) for comment.

Recommendation (circle one): (File) RTF

Pharm/Tox reviewer: Hong Zhao 12/10/02
(signature/ date)

Branch Chief concurrence: Martin D. Green 1/7/03
(signature/ date)

Division. Director concurrence: [signature] 1-21-03
(signature/ date)

Chen (B)

STN 103770/5033 Product Palivizumab

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
◻ Biopharmaceutics and associated analytical methods	Y	N	
◻ Clinical pharmacology [includes immunogenicity]	Y	N	
◻ Clinical Efficacy [for each indication]	Y	N	
◻ Clinical Safety	Y	N	
◻ Synopses of individual studies	Y	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
◻ Biopharmaceutic	Y	N	
◻ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
◻ Pharmacokinetics (PK)	Y	N	
◻ Pharmacodynamic (PD)	Y	N	
◻ Efficacy and Safety	Y	N	
◻ Postmarketing experience	Y	N	
◻ Case report forms	Y	N	
◻ Individual patient listings (indexed by study)	Y	N	
o electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y	N	
◻ legible	Y	N	
◻ English (or certified translation into English)	Y	N	
◻ compatible file formats	Y	N	
◻ navigable hyper-links	Y	N	
◻ interpretable data tabulations (line listings) & graphical displays	Y	N	

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BIMo sites identified?		
MI-CP048	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Is clinical site(s) inspection (BiMo) needed?

NO

Is an Advisory Committee needed?

NO

Recommendation (circle one): File RTF

Reviewer _____ 1-6-03 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: _____
(signature/ date) (signature/ date)

1-6-03 1-6-03

Forsyth (C)

supplemental BLA

STN 103770/5033 Product SYNAGIS (PALIVIZUMAB)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y)	N	
▫ Biopharmaceutics and associated analytical methods	Y	(N)	
▫ Clinical pharmacology [includes immunogenicity]	(Y)	N	Immunogenicity not assessed in this study.
▫ Clinical Efficacy [for each indication]	(Y)	N	
▫ Clinical Safety	(Y)	N	
▫ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	(Y)	N	
▫ Biopharmaceutic	Y	(N)	
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y)	(N)	
▫ Pharmacokinetics (PK)	Y	(N)	
▫ Pharmacodynamic (PD)	Y	(N)	
▫ Efficacy and Safety	(Y)	N	
▫ Postmarketing experience	Y	N	
▫ Case report forms	(Y)	N	
▫ Individual patient listings (indexed by study)	(Y)	N	Paper submission.
o electronic datasets (e.g. SAS)	(Y)	N	will request PDF files of sections of the BLA (eg. clinical study report to be submitted.
Literature references and copies [5.4]	(Y)	N	

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
▫ legible	(Y)	N	
▫ English (or certified translation into English)	(Y)	N	
▫ compatible file formats	(Y)	N	
▫ navigable hyper-links	Y	(N)	only stat SAS files included electronically.
▫ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	n/a
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	n/a
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	n/a
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	n/a
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure of investigators submitted?			SAS & other electronic datasets complete & usable?		DMC Sites Required?		
M1-GP048	(Y)	N	(Y)	N	NR	(Y)	N	Y	(N)	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

NO.

Recommendation (circle one): (File) RTF

Reviewer: Linda M. Yancey 1/7/03 Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: Jeffrey A. Boswell 1/7/03 Division. Director:
(signature/ date) (signature/ date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 6, 2003

From: Dale C. Slavin, Regulatory Project Manager, OTRR/DARP 1-6-03

Subject: First Committee Meeting for MedImmune Palivizumab STN 103770/5033
A study evaluating Palivizumab in pediatric patients with congenital heart disease.

To: Attendees

Meeting Date: December 10, 2003 ; 4005 WOC1

Yuan Who Chen	Biostats
Estella Z. Jones	Clinical Site Inspector
Dale Slavin	RPM
Hong Zhao	Clinical Pk/Pd

This was the internal first committee meeting for the 10 month PAS for Palivizumab. No major deficiencies were cited. The filing review memo and checklist was handed out to each member and they were requested to fill out their appropriate portion in time for the filing meeting to be held on January 7, 2003. Additional analyses of the data in regards to the impact of gender and age upon the administration of Palivizumab in congenital heart disease patients will be requested from MedImmune. There were no other issues identified at this meeting.
Linda Forsyth (Clinical) was unavailable but on December 12, 2002 she had no issues to relay to the committee.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Slavin, Dale

From: Jones, Karen
Sent: Monday, September 15, 2003 10:46 AM
To: Davis, Robert (CBER)
Cc: Thurber, Steven; Rivera Martinez, Edwin; Slavin, Dale
Subject: Emergency Compliance Check for Medimmune Palivizumab STN 103770/5033

Importance: High

Follow Up Flag: Reply
Due By: Monday, September 15, 2003 4:00 PM
Flag Status: Flagged

Good morning,

On behalf of Dale Slavin, an RPM in CDER/OTRR/DARP, I am submitting an **emergency request for a compliance check for the following BLA supplement approval that is needed for TODAY, 9/15/03. We apologize for the very short turn-around time for this request. The need for a compliance check was overlooked. If there is anything you can do to provide the check today, we would be most appreciative. If you are able to complete the check, please send your response to Dale Slavin.**

Medimmune, Inc.
Palivizumab (proprietary name is Synagis)
STN 103770/5033

This BLA supplement is an efficacy sBLA for an expanded indication that includes children with hemodynamically significant congenital heart disease. There are no manufacturing or facility changes associated with this supplement.

The facilites involved with the manufacture of this product are:

MedImmune, Inc.

(b) (4)

(b) (4)

(b) (4)

Thank you.

Karen Jones, RPM
Acting Branch Chief
CDER/OTRR/DARP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: August 28, 2003

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

Lou Marzella and myself called Julia Goldstein regarding the AE table on page 10 of the PI. Louis requested that MedImmune supply a complete listing of all AE incidences by trial and also a complete listing of pooled AEs and pools of all AEs as incidence. Julia agreed to submit the data.

103770/5033

Slavin, Dale

m: Forsyth, Linda
t: Friday, August 01, 2003 1:52 PM
To: Slavin, Dale
Subject: MedImmune telecon memo

Dale:

Attached is a memo of the telecon with MedImmune 7-31-03.

Linda

Palivizumab telecon 7-31-03.do...

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: July 31, 2003

FROM: L. Forsyth

SUBJECT: Teleconference record

TO: File

FDA representatives:
Dr. Bo Zhen-Biostatistician
Dr. Linda Forsyth-Clinical
Dr. Jeffery Siegel-Clinical acting Branch Chief

Sponsor representatives:
Dr. Dave Carlin, VP, Biostatistics
Dr. Ed Connor, Sr. VP Clinical Development
Melia Grim, Regulatory Affairs Manager
Dr. Genevieve Losonsky, Director, Clinical Development
Dr. Paul Mendelman, VP Clinical Research
Dr. Peter Patriarca, VP Regulatory Affairs

Summary:

Teleconference was held with MedImmune on Thursday, July 31, 2003 at 3:00 p.m. with FDA representatives and the MedImmune representatives listed above to discuss issues raised at the midcycle review of the Palivizumab supplemental biologics license application for prophylaxis of Respiratory Syncytial Virus in children with congential heart disease. The issues discussed with the sponsor include:

1. Financial disclosure. Please provide a list of investigators who have financial interest in the study. If none, please state so.

2. Summary of hospitalization by cyanotic strata. (Exhibit 32 p.72 of clinical report, Summary of Hospitalizations.) Please repeat table and stratify further by cyanotic and non-cyanotic.

3. Baseline demographics by cyanotic strata.

4. Compare number of days of RSV hospitalization, incidence of ICU admission and total RSV days with increased supplemental oxygen between the treatment groups

among patients with RSV hospitalization incident. (Exhibit 30 p. 70 of clinical report)

5. Number of Patients with RSV Hospitalization by Months on Study.

6. Please provide tables combining the adverse events in this study with the data from the previous study. (Exhibit 51 and 52 of clinical report, AEs >=1%.)

7. The levels of palivizumab falls after surgery requiring cardiopulmonary bypass. What recommendations would you make to clinicians about dosing of patients undergoing cardiopulmonary bypass? (Exhibit 36 p. 76 of clinical report)

8. [redacted] (b) (4)

The sponsor agreed to address all of the above issues and will send an amendment to the agency responding in writing to each of these issues. The sponsor indicated they would be able to conduct all requested analyses and will attempt to make label suggestions for the agency. The sponsor anticipates they will be able to complete these requests by next week.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: March 25, 2003

From: Richard Chen, Ph.D., OTRR/DRMP ywc

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

I called Julia Goldstein, MD of MedImmune and requested a new SAS transport file for MI CP048. This file should include:

Patient ID, year of entry, treatment group, age, gender, ethnic group, weight at entry, country, stratum, completion status or reason for termination, total days of RSV hospitalization and mechanical ventilation and in ICU as well as total days of increased O2. Please combine demographic, endpoint and RSV risk factor variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 24, 2003

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

I called Julia Goldstein and requested that she submit the appropriate wording for the Debarment statement. She agreed to do so.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103770/5033

JAN 2 3 2003

Peter Patriarca, M.D.
MedImmune, Incorporated
35 West Watkins Mill Road
Gaithersburg MD 20878

Dear Dr. Patriarca:

This letter is in regard to the supplement to your biologics license application for Palivizumab to revise the package insert to include efficacy, pharmacokinetic, and safety data in patients with congenital heart disease submitted under Section 351 of the Public Health Service Act.

While conducting our filing review, we identified the following potential review issue:

> Please submit further analyses on serum Palivizumab concentrations to determine the effects, if any, race, gender, age, weight or concomitant medication has on Palivizumab systemic exposure.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Dale Slavin, at (301) 827-5101.

Sincerely yours,

Dale C. Slavin, Ph.D.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

OTRR/DARP/Slavin/1-14-03/:K.Townsend:1.21.2003:1.23.2003
(S:\Slavin\Letters\BLA\Palivizumab\Backup of D74)

COMMUNICATION TYPE:

LETTER: **OTHER (OT)**

Summary Text: 74 Day Review

SS Data Check:
- **Communication**

Division	Name/Signature	Date
DARP		1-23-03
DARP	Kelly Townsend	1-24-03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103770/5033

JAN 14 2003

Peter Patriarca, M.D.
MedImmune, Incorporated
35 West Watkins Mill Road
Gaithersburg MD 20878

Dear Dr. Patriarca:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your supplement dated November 14, 2002, for Palivizumab to determine its acceptability for filing. This supplement is for revising the package insert to include efficacy, pharmacokinetic, and safety data in patients with congenital heart disease. In accordance with 21 CFR 601.2(a), the supplement is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the supplement, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Dale Slavin, at (301) 827-5101.

Sincerely yours,

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: HFM-585/DARP BLA file
HFM-588/D. Slavin
HFM-582/L. Forsyth

CBER:DARP:Slavin: 1-8-03:K.Townsend:1.10.2003:1.14.2003
(S:\Slavin\letters\BLA\Palivizumab\FL.103770.5033)

COMMUNICATION TYPE:
LETTER: Filing Notification (FL)

SS Data Check:
- **Communication**
- **Milestone: Confirm Filing Action Entry & Closed Date**

Division	Name/Signature	Date
DARP		1-14-03
DARP	Dye for Jones	1-14-03
DARP	Kelly Townsend	1-14-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 9, 2003

From: Dale Slavin, Ph.D., Regulatory Project Manager OTRR/DARP

Subject: Extra Copy Request of final study report for clinical study MI-CP048

To: FDA BLA 103770/5033 file

On January 9, 2003, I contacted Megan Moncur of MedImmune regarding their November 14, 2002 submission. I requested an additional copy of volume one of the submission.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 8, 2003

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

I called Julia Goldstein and requested that if possible could she send an electronic copy of the clinical study report. She agreed to do so.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

000802448

NOV 26 2002

Peter Patriarca, M.D.
MedImmune, Inc.
35 West Watkins Mill Road
Gaithersburg, Maryland 20878

Dear Dr. Patriarca:

SUBMISSION TRACKING NUMBER (STN) BL 103770/5033 has been assigned to your recent supplement to your biologics license application for Palivizumab, received on November 15, 2002, to revise the package insert to include efficacy, pharmacokinetic, and safety data in patients with congenital heart disease.

All future correspondence or supportive data relating to this supplemental application should bear the above STN and be addressed to the Director, Division of Application Review and Policy, Office of Therapeutics Research and Review, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20852-1448.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need to discuss the technical aspects of this supplement, you may obtain the name of the chairperson of the review committee by contacting this division at 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this division.

Sincerely yours,

Carl Deye

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: DARP BLA File, HFM-588
William Tauber, HFM-570
Dale Slavin, HFM-588

OTRR/DARP:K.Townsend:11.20.2002
S:\STN 2002\103770.5033.PAS.doc

COMMUNICATION TYPE:

LETTER: Acknowledgment Letter (ACK)
Summary Text: STN Assignment – Pre Approval (PAS)

SS & RIS Data Check:

- **If "Unacceptable for Filing (UN)" add under LETTER.**
- **Communication**
- **Verify inclusion of Option 1 paragraph for manufacturing supplmts *(if Alt. 6 is not used).***

RIS Data Check:

- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

Division	Name/Signature	Date
DARP		11-22-02
DARP		11-26-02
DARP		11-26-02
DARP	Kelley Townsend	11-26-02

BLA/NDA/PMA
Review Committee Assignment Memorandum

X Initial Assignment
❑ Change

BLA: 103770/5033

Applicant: MedImmune, Inc.

Product: Palivizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Dale Slavin	Reg. Coordinator	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
Linda Forsyth	Reviewer	Clinical	Jeffrey Siegel	11-25-02
		Product		
		Product		
		Clinical		
		Clinical		
Hong Zhao	Reviewer	Clinical Pharmacology	Dave Green	11-25-02
		Pharm/Tox		
Yuan Who Chen	Reviewer	Biostatistics	G. Gupta	11-25-02
		BiMo		
		Epidemiology		
		Facility		
Estella Z. Jones	Reviewer	Inspector	Robert Leedham	11-25-02
		Labeling		
		Other		

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
William Tauber	Reviewer/Chair	Clinical	Weiss/Siegel	11-25-02

* **reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Dale Slavin — Name Printed
Signature
11-27-02 — Date

Memo entered in RMS by: P.H Date: 11-27-02 QC by: SJO Date: 12/2/02

S:\DARP\FORMS\BLA Committee Assignment.doc
Final: 4/16/02; 4/18/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: November 20, 2002

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

I called Julia Goldstein and explained to her that the financial disclosure was necessary for this submission including the financial interests of all physicians. She agreed to submit the financial disclosure information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: November 20, 2002

From: Dale Slavin, Ph.D., OTRR/DRMP

Subject: Teleconference with Julia Goldstein, MD

To: BLA STN: 103770/5033

I called Julia Goldstein and requested that she submit both electronic versions of the PI as well as hard copies of the PI both redlined and clean copies were necessary for the electronic copy. I also requested to additional copies of the 28 volume original submission. She agreed to submit all the requested information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: November 20, 2002

From: Karen Weiss, M.D., HFM-570

Subject: Designation of Priority for BLA Supplement Review
Sponsor: MedImmune.
Product: Palivizumab
Supplement: To revise the Package insert to include efficacy pharmacokinetics and safety data in patients with congenital heart disease.

To: BLA Supplement 103770/5033

The review status of this file, when submitted as a BLA, is designated to be:

☐ 6 month priority

☒ 10 month standard