CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103770/S-5059

Trade Name: **SYNAGIS**

Generic Name: **Palivizumab**

Sponsor: **MedImmune, Incorporated**

Approval Date: 12/14/2004

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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

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APPLICATION NUMBER:

BLA 103770/S-5059

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103770/5059

MedImmune, Incorporated
Attention: Peter Patriarca, M.D.
Vice President, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20898

Dear Dr. Patriarca:

Your request to supplement your biologics license application for Palivizumab, to provide 50 mg and 100 mg liquid formulations in single-dose vials has been approved.

The dating period for Palivizumab liquid formulation drug product shall be 24 months from the date of manufacture when stored at 2-8 degrees C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 9 months when stored at 2-8 degrees C. We have approved the stability protocol SP-76107 in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We acknowledge your written commitment to conduct a postmarketing study as described in your letter of July 9, 2004, outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

To conduct an immunogenicity study, MEDI-493, entitled "A Phase IV, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilized Formulations of Palivizumab in Children at High Risk for the Development of Serious RSV Disease." You will submit validation of the bioassay prior to conducting the immunogenicity study. The final protocol for this study will be submitted by April 30, 2005, and patient accrual will be completed by December 31, 2005. The study will be completed by October 31, 2006, and the final study report will be submitted by April 30, 2007.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103770. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 103770. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

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/cder/biologics/default.htm. 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,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

(b)(5)

cc: HFM-585/ DARP BLA file
HFM-561/ S. Kozlowski
HFM-555/ P. Swann
HFM-500/ OTRR Office Director
HFM-672/ Product Release Staff Director, HFM-672 (if non-specified product)
HFD-322/ E. Rivera-Martinez, IPCB
HFM-4/ QAS
HFM-110/ RIMS
HFM-670/ DMPQ Blue file
HFD-320/DMPQ Division Director
HFM-599/ M. Smedley
HFM-599/ C. Renshaw
HFM-599/ J. Kutza

History: (b)(4) -- --------: 7.23.04

File Name: (b)(4) -----103770.5059/061704.approval letter

Office	Name/Signature	Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

LABELING

07-24-04-Final Draft sent to the sponsor

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 available in two formulations: a lyophilized powder and a liquid solution.

Lyophilized Powder: Synagis® is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® (100 mg/mL) is to be administered by intramuscular injection (IM) only. The reconstituted solution should appear clear or slightly opalescent with pH of 6.0.

Each 100 mg single-use vial of Synagis® lyophilized powder is formulated in 67.5 mg of mannitol, 8.7 mg histidine and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis® in 1.0 mL when reconstituted with 1.0 mL of sterile water for injection.

Each 50 mg single-use vial of Synagis® lyophilized powder is formulated in 40.5 mg mannitol, 5.2 mg of histidine and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis® in 0.5 mL when reconstituted with 0.6 mL of sterile water for injection.

Liquid Solution: Synagis® (100 mg/mL) is supplied as a sterile, preservative-free solution to be administered by intramuscular injection (IM) only. The solution should appear clear or slightly opalescent with pH of 6.0.

Each 100 mg single-use vial of Synagis® liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of glycine in a volume of 1.2 mL to and is designed to deliver 100 mg of Synagis® in 1.0 mL.

Each 50 mg single-use vial of Synagis® liquid solution is formulated in 2.7 mg of histidine and 0.08 mg of glycine in a volume of 0.7 mL to and is designed to deliver 50 mg of Synagis® in 0.5 mL.

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®.

Trough serum Synagis® concentrations were comparable between the Synagis® liquid and Synagis® lyophilized formulations administered IM at 15 mg/kg in a cross-over trial in 153 pediatric patients ≤6 months of age with a history of prematurity.

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	N	500	1002			
Impact-RSV	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55	<0.001
Trial 2	n	648	639			
CHD	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. Lyophilized Synagis® must be used within 6 hours of reconstitution. Administration of either reconstituted Synagis® or liquid Synagis® should occur immediately after withdrawal from vial. 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. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis® in Trials 1 and 2.

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.

OVER DOSAGE: No data from clinical studies are available on over dosage. 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 of Lyophilized Product 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 tilted slightly and gently rotated for 30 seconds to avoid foaming. DO NOT SHAKE or VIGOROUSLY AGITATE the VIAL. This is a critical step to avoid prolonged foaming.
- Reconstituted Synagis® should stand undisturbed 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 (a thin layer of micro-bubbles on the surface is normal and will not affect dosage). 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. Administer immediately after withdrawal from vial. Synagis® is supplied in single-use vials DO NOT re-enter the vial. Discard any unused portion.

Preparation of Liquid Product for Administration:

- 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.
- Synagis® does not contain a preservative and should be administered immediately after withdrawal from vial. 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 available in two formulations: a lyophilized powder and liquid solution.

Lyophilized Powder: 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.

Liquid Solution: Synagis® is supplied in single-use vials as a preservative free, sterile solution at 100 mg/mL in 0.5 mL and 1.0 mL to deliver either 50 milligrams or 100 milligrams, respectively for IM injection.

50 mg vial NDC 60574-4114-1
The 50 mg vial contains 50 milligrams Synagis® in 0.5 mL.

100 mg vial NDC 60574-4113-1
The 100 mg vial contains 100 milligrams Synagis® in 1.0 mL.

Upon receipt and until 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:

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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.
3. Bentley D, and Rabbitts T. Human immunoglobulin variable region genes - DNA sequences of two Vκ genes and a pseudogene. Nature 1980; 288:730-733.
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.
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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: Co-Marketed by:

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

Ross Products Division
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Columbus, OH 43215-1724

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

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

June 30, 2004

From: William B. Tauber, M.D.

Through: Louis Marzella, M.D. Team Leader, DTBIMP, ODE VI

Marc Walton, M. D. Division Director, DTBIMP, ODE VI

To: STN 103770/5059

Topic: Clinical Review

Biologic License Application: STN 103770/5059

Product: Palivizumab (Synagis®)

Indication: Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease.

Sponsor: MedImmune Corporation

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Review for Label Supplement STN # 103770/5059 Label Changes for Synagis®

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on the clinical safety data, and the revised PI, the reviewer recommends that the labeling supplement seeking to market a liquid formulation of Synagis (in addition to the existing lyophilized formulation) be approved.

(b) (4)

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Synagis® (palivizumab) was approved for the prevention of lower respiratory infection due to Respiratory Syncytial Virus (RSV) in pediatric patients at risk for severe RSV infection in 1998. Synagis is supplied as a lyophilized formulation that requires reconstitution prior to IM injection. In this license application supplement, the sponsor seeks the approval of a liquid formulation of Synagis to be marketed in addition to the lyophilized formulation.

The submission contains biochemical data and pharmacokinetic clinical data that in judgment of the FDA product and pharmacology reviewers showed the liquid and lyophilized formulations to be comparable. The objective of the clinical review was to assess the human safety, tolerability, and Immunogenicity of the two formulations in two clinical studies.

The sponsor conducted two clinical studies under IND 5862 to examine the comparability of the human safety, tolerability, immunogenicity and pharmacokinetics (PK) characteristics of the liquid and the lyophilized preparations

of Synagis. The first study, MEDI-CP080 was conducted between 6 June 2001 and 25 August 2001 comparing two doses IM and single dose IV of both liquid and lyophilized product in 48 healthy adults using a 4 armed parallel design. The second study, MEDI-CP097 conducted between 01 November 2002 and 04 April 2003 compared identical doses of the liquid and lyophilized product administered to 153 infants ≤ 6months of age with a history of prematurity using a cross-over design. This cross-over design exposed all study participants to both the liquid and the lyophilized product. Participants were randomized to either Sequence A which administered liquid palivizumab at day 0 and lyophilized palivizumab at day 30 or to Sequence B which administered lyophilized palivizumab at day 0 and liquid palivizumab at day 30.

The data generated by these two clinical studies does not indicate a significant difference between the safety, and tolerability of the liquid palivizumab compared to the licensed lyophilized palivizumab. Although immunogenicity data submitted does not demonstrate the presence of significant anti-palivizumab antibodies, the potential for interference by residual palivizumab at the time of immunogenicity testing precludes conclusions regarding the immunogenicity of the liquid formulation.

B. Efficacy

The primary objective of the two clinical studies was to assess the PK comparability and safety of the liquid and lyophilized formulations of palivizumab. The studies were not designed to assess clinical efficacy.

C. Safety

1. Study MEDI-CP080 demonstrated similar numbers, type and severity of adverse events in adults receiving the liquid formulation and in adults receiving the lyophilized formulation of palivizumab. The only difference was a higher incidence of dizziness associated with the liquid formulation administered either IM (n=3) or IV (n=2) compared with the lyophilized formulation (n=0). Review of these five events indicates that all were mild and transient; none required any treatment and two of the events were associated with either venopuncture or pain at injection site.

2. In Study MEDI–CP080 low level anti-palivizumab antibodies developed in 20 of the 48 adult volunteers receiving either formulation IM or the liquid formulation IV. In all cases, the antibody titers remained stable or diminished between the first and the second injection. The sponsor interpreted these results to mean that anti-idiotype antibodies were being measured. The sampling was done during time intervals when palivizumab was likely to have been present raising the potential for test interference.
3. In Study MEDI-CP097, the incidence of all adverse events between the two subgroups dosed in Sequences A (liquid followed by lyophilized) and B (lyophilized followed by liquid) appeared similar between the two preparations both in the period following each injection as well as for the entire 60 days of the study. Most of the adverse reactions were mild and typical for a population of premature infants. The only adverse event that appeared to show a 3% or higher difference between the groups in both study periods and over the entire study was nervousness (irritability). There were 6 (3.9%) instances of nervousness-irritability, all occurring with the liquid preparation, all were treated. There were no instances of nervousness-irritability associated with the lyophilized preparation. Further exploration of the patient listings determined that all 6 of the cases of irritability occurred in association with other adverse events such as bilateral otitis media, abdominal gas, teething pain, cough. In addition, there were two instances of untreated irritability noted in the comments column of the listings both associated with fever and both following receipt of lyophilized palivizumab. This would seem to further lessen the significance of the apparent imbalance between the liquid and the lyophilized preparation.
4. In study MEDI-CP097, the incidence of children with at least one serious adverse events was similar between the liquid formulation (5 children [3.3%] each with one serious adverse event) and the lyophilized formulation (4 children [2.6%] with a total of 5 serious adverse events). Adverse events requiring medical intervention were also similar after liquid palivizumab administration (34%) and lyophilized palivizumab administration (31%).
5. In Study MEDI-CP097, 126 (83%) of infants were evaluated for the presence of anti-palivizumab antibodies. Among those evaluated, 2 (one from each Sequence) were noted to have binding activity greater than 1:10 at Study Day 60. The sampling in this study was also done during time intervals when palivizumab was likely to have been present which raises the potential for test interference.

D. Dosing

The dose of palivizumab recommended in the package insert is 15mg/kg. This dose was selected for both liquid and lyophilized palivizumab given intravenously to the adult volunteers in study MEDI-CP080 and to all

participants in MEDI-CP097 intramuscularly. In MEDI-CP080, volume considerations for adult subjects lead to a reduction to 3mg/kg of both the liquid and the lyophilized palivizumab given intramuscularly.

E. Special Populations

The population selected for study in MEDI-CP097 was premature infants younger than 6 months of age which corresponds to one of the age groups specifically mentioned in the current package insert as meeting an indication for palivizumab administration. There is no concern that study of this group would not be applicable to the remainder of the indicated population of pediatric patients at high risk of RSV disease [redacted] (b) (4) As risk of severe RSV disease diminishes with age greater than 24 months, it is reasonable to consider a waiver for study of the liquid formulation in pediatric patients older than 24 months.

Clinical Review

I. INTRODUCTION AND BACKGROUND

A. Respiratory syncytial virus (RSV) infection presents a large public health burden in the U.S. and worldwide. RSV infections occur during yearly seasonal outbreaks lasting from late autumn through early spring in the U.S. and other temperate-zone countries. RSV illness is estimated to result in 50-80,000 hospitalizations and 500 deaths annually in the U.S. Infants and children with prematurity, bronchopulmonary dysplasia (BPD), or congenital heart disease (CHD) are particularly vulnerable to more severe disease following RSV infection.

Palivizumab (Synagis®) is an F-protein-specific humanized monoclonal antibody, which neutralizes a broad range of RSV isolates. Palivizumab has been studied in children with prematurity or BPD and shown to be safe and effective at a dose of 15 mg/kg monthly; reducing the incidence of RSV associated hospitalizations by 55% , 4.8% of palivizumab recipients versus 10.6% of placebo recipients. Palivizumab was licensed in 1998 by the FDA for use in the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. Including the U.S., palivizumab is currently being distributed and used in 53 countries worldwide.

B. Synagis is supplied as a lyophilized product. Reconstitution of lyophilized palivizumab takes approximately 20 minutes. MedImmune has developed a liquid formulation of palivizumab to avoid the need for reconstitution.

II. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY,

BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

This submission does not contain animal pharmacology or toxicology data. The product characterization data showed evidence of comparability of the liquid and lyophilized formulations (See the FDA product review).

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Measurements of pharmacokinetic parameters established the comparability of the two formulations. (See FDA pharmacology review).

IV. DESCRIPTION OF CLINICAL DATA AND SOURCES

A. OVERALL DATA

The sponsor provided the full and final study reports of both clinical studies MEDI-CP080 and MEDI-CP097 and these will be described below.

B. CLINICAL TRIALS LISTS

Studies from which data submitted

1. **MEDI-CP080**
   A. Phase 1, double blind, randomized, healthy adult volunteers conducted at 2 sites. This study began enrollment 06 June 2001 and last study visit was completed 25 August 2001. A total of 48 volunteers were studied, 12 in each of the four treatment groups. For this submission, the full and final study report was submitted.
2. **MEDI-CP097**
   A. Phase 2, randomized, double-blind, two-period, cross-over study comparing the pharmacokinetics, safety, and tolerability of the liquid formulation of palivizumab with those of the lyophilized formulation. A total of 153 children were randomized into the study between 01 Nov 2002 and 03 Feb 2003 at 21 sites in the US. For this submission, the full and final study report was submitted.

C. POSTMARKETING EXPERIENCE

Data from post-marketing experience is not submitted with this application.

D. LITERATURE REVIEW

No specific safety issues associated with the use of liquid SYNAGIS were identified in a literature search using the search terms, "liquid palivizumab and RSV infection" or "synagis liquid" in PubMed by the clinical reviewer.

V. CLINICAL REVIEW METHODS

A. Describe How Review was conducted

The two clinical trial study reports were reviewed with respect to safety. The FDA pharmacologists' and product reviewer's reviews were considered.

B. Overview of Materials Consulted in Review

The sponsor provided the full and final study reports of both clinical studies MEDI-CP080 and MEDI-CP097.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The numbers and importance of protocol violations, discontinuation of patients from study and missing data were evaluated for the two studies. The evidence was consistent with a well conducted trial. It was determined that inspection of study sites was not needed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Data were extracted from clinical studies conducted under acceptable ethical standards. Applicable patient safeguards including Informed consent and IRB review and oversight of the protocols were applied.

E. Evaluation of Financial Disclosure

The sponsor provided certification of absence of financial interests and arrangements of clinical investigators, FDA Form 3454, for both clinical studies.

VI. INTEGRATED REVIEW OF EFFICACY

A. Conclusions

This submission contained no efficacy data. The primary objectives of this clinical program were to establish the comparability of liquid and lyophilized formulations of palivizumab by pharmacokinetic criteria and to compare the safety experience with the two formulations. Study MEDI-CP080 demonstrated that liquid palivizumab administered to healthy adults by either the IM or IV route had similar pharmacokinetics at the same doses to lyophilized palivizumab. This was a descriptive analysis only. In Study MEDI-CP097 pharmacokinetic comparability of the proposed liquid and the marketed lyophilized palivizumab was demonstrated, based on the ratios of least squares geometric means of through serum palivizumab concentrations for the two palivizumab formulations and the 90% confidence intervals for these ratios. (See the FDA pharmacologists review).

B. General Approach to Review of the Efficacy of the Drug

The clinical studies were not designed to assess the efficacy of the palivizumab liquid formulation. The findings of the FDA's pharmacologist's review were considered and are summarized in this document.

C. Detailed Review of Trials by Indication

The objective of this labeling supplement was to provide pharmacokinetic and safety data to establish comparability of the two palivizumab formulations, liquid and lyophilized. For complete description of the study design, pharmacokinetic endpoints, subject demography and study conduct of the two clinical studies submitted in this application, please see section VII C. Methods and Specific Findings of Safety Review.

D. Efficacy Conclusions

The main objective of the studies was to establish the comparability of the liquid and lyophilized formulations by pharmacokinetic criteria. For detailed discussion of the pharmacokinetic data examining comparability of the liquid and lyophilized formulation of palivizumab please see FDA pharmacology review.

VII. INTEGRATED REVIEW OF SAFETY

A. Brief Statement of Safety Conclusions

The adverse events observed in patients receiving the liquid formulation of palivizumab were similar in frequency and severity to those observed in patients receiving the licensed lyophilized formulation. This safety profile was consistent with that observed in the registration trials. Immunogenicity testing was performed in both clinical studies. Among adult volunteers, 20/48 had detectable antibodies to palivizumab which were mostly low titer, fell during the study and did not increase with re-administration of palivizumab. Among the pediatric patients, 2 patients, one in each sequence developed anti-palivizumab antibodies >1:10 The Immunogenicity data for both studies was judged to be inconclusive because of the sampling intervals chosen.

B. Description of Patient Exposure

The dosage of palivizumab recommended in the package insert is 15mg/kg intramuscularly. Adults in study MEDI-CP080 received either 2 intramuscular injections of 3mg/kg of either liquid or the lyophilized formulation of palivizumab at day 0 and 30 or one intravenous injection of 15mg/kg of either liquid or the lyophilized formulation of palivizumab at day 0. Administered volume concerns prompted the lower IM doses and the intravenous route for the recommended dosage in the adult volunteers. Patients in study MEDI-CP097 received the recommended dosage of either the liquid or the lyophilized formulations in two injections, one at day 0 and the other day 30.

C. Methods and Specific Findings of Safety Review

The reviewer examined the full and final study reports, and adverse events listings

STUDY MEDI-CP080

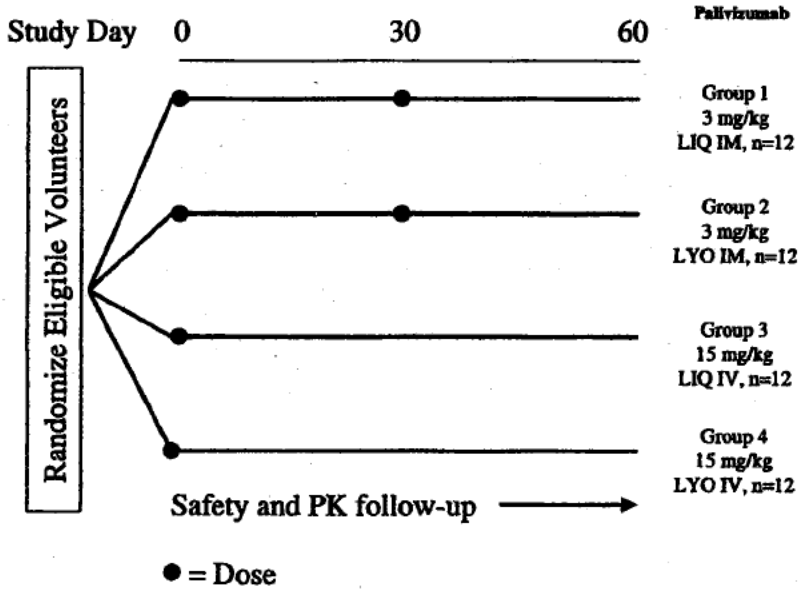
MEDI-CP080

Study Design

Phase I, double blind, randomized, PK study of healthy adult volunteers conducted at 2 sites **(Figure 1)**. Volunteers were randomized to one of 4 parallel groups at two sites. The study drugs were liquid (LIQ) palivizumab and the currently licensed lyophilized (LYO) palivizumab
GROUP 1: N=12 3 mg/kg LIQ palivizumab at Study Days 0 and 30, IM
GROUP 2: N=12 3 mg/kg LYO palivizumab at Study Days 0 and 30, IM
GROUP 3: N=12 15 mg/kg LIQ palivizumab at Study Day 0, IV
GROUP 4: N=12 15 mg/kg LYO palivizumab at Study Day 0, IV

Figure 1 Flow Chart Study Design MEDI-CP080

FLOWCHART OF STUDY DESIGN



Primary Pharmacokinetic Endpoints

The *in vivo* pharmacokinetics of 15 mg/kg palivizumab administered IV were evaluated by the following parameters:

- Cmax: Maximum serum concentration;
- T½: Elimination half-life;
- C_{trough}: Serum concentration at 30 days after administration;
- AUC_{0-30}: Area under the serum concentration-time curve to Study Day 30;
- V_d: Volume of distribution; and
- CL_t: Total clearance.

Secondary Pharmacokinetic Endpoints

The *in vivo* pharmacokinetics of 3 mg/kg palivizumab administered IM were evaluated by the following parameters:

- Cmax: Maximum serum concentration;
- T½:: Elimination half-life;
- C_{trough}: Serum concentration at 30 days after administration;
- AUC_{0-30}: Area under the serum concentration-time curve to Study Day 30;
- V_d: Volume of distribution; and
- CL_t: Total clearance.

Study conduct

Anticipated enrollment for this study was 48 and 60 volunteers were randomized for participation at the two study sites. An initial group of 12 volunteers was randomized into the IV treatment group at Site 2. Technical difficulties with the IV infusion at Site 2 resulted in partial dosing (< 50% of calculated dose administered)

in 5 volunteers and cancellation of the remaining 7 who did not receive any study drug. An investigation revealed problems with the type of in-line filter used. The filter was replaced and an additional 12 volunteers were randomized and study drug was administered. The 5 who received partial doses of the study drug were followed through Study Day 7 for safety and then withdrew consent for further follow-up. The sponsor states that these 5 did not experience any adverse events during this 7 day period and their data is not included in the safety data in this submission. All volunteers other than the 12 discussed above received the scheduled dosages of study drug. 46 of the 48 volunteers who received full dose of study drug participated in the study through day 60. 2 volunteers did not, one withdrew consent due to unanticipated family travel and the other was lost to follow-up **(Table 1).** Neither was stated to have withdrawn for adverse events.

Table 1 Summary of Status of Enrolled Volunteers at Study Day 60

Disposition	Palivizumab			
	3 mg/kg IM		15 mg/kg IV	
	LIQ (N=12)	LYO (N=12)	LIQ (N=12)	LYO (N=12)
Completed Study	12 (100.0%)	12 (100.0%)	12 (100.0%)	10 (83.3%)
Discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
Lost to Follow-Up	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Withdrawal of Consent	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)

Volunteer Demography

A majority of volunteers in each treatment group were female. The racial composition of the volunteer population was 56% Caucasian, 25% Hispanic, 17% African American and 2% Asian. Mean height, weights and ages were similar across all four treatment groups **(Table 2).**

Table 2 Summary of Demographic Data

Characteristic	Palivizumab			
	3 mg/kg IM		15 mg/kg IV	
	LIQ (N=12)	LYO (N=12)	LIQ (N=12)	LYO (N=12)
Sex				
Male	4 (33.3%)	3 (25.0%)	5 (41.7%)	4 (33.3%)
Female	8 (66.7%)	9 (75.0%)	7 (58.3%)	8 (66.7%)
Age (Years)				
N	12	12	12	12
Mean (SE)	32.4 (2.5)	32.7 (2.5)	32.4 (2.4)	30.3 (2.2)
Min-Max	20.5-45.3	20.7-48.5	21.3-42.3	19.3-42.5
Race				
Caucasian	4 (33.3%)	6 (50.0%)	7 (58.3%)	10 (83.3%)
Black	2 (16.7%)	3 (25.0%)	2 (16.7%)	1 (8.3%)
Hispanic	5 (41.7%)	3 (25.0%)	3 (25.0%)	1 (8.3%)
Asian	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)				
N	12	12	12	12
Mean (SE)	165.6 (2.7)	168.1 (2.9)	169.0 (3.6)	170.3 (3.2)
Min-Max	155-180	155-188	151-185	156-189
Weight (kg)				
N	12	12	12	12
Mean (SE)	71.3 (3.9)	72.3 (4.1)	69.2 (4.2)	71.2 (4.2)
Min-Max	54.0-97.7	59.2-100.2	48.9-100.2	53.5-96.2

Protocol Deviations

Volunteer 363211 in the IM liquid palivizumab group received an oral corticosteroid (methylprednisolone) for 5 days without the sponsor's knowledge 27 June 2001-01 July 2001 for the treatment of adverse event (left knee pain of unknown cause). Study drugs were administered 10 June 2001 and 10 July 2001

Adverse Events

All Adverse Events:

Adverse events for all volunteers who received a complete dose of study drug are summarized in **Table 3.** The sponsor states that 93% of the adverse events were mild and that none were severe. Three volunteers in the IM liquid group (363221, 468109, and 468124) experienced mild, transient dizziness. This dizziness occurred with the first injection, did not recur with the second injection and did not require any treatment. There were no instances of dizziness in the IM lyophilized group. In addition, two volunteers in the IV liquid palivizumab group (363228, 468117) also experienced mild, transient dizziness not requiring treatment again versus none in the IV lyophilized preparation. In patient 363228, the dizziness occurred in association with pain at the injection site. Three volunteers in the IM liquid group (363201, 363206, and 363211) versus one in the IM lyophilized group developed mild transient injection site pain. Patient 363228 of the IV liquid palivizumab group experienced injection site pain versus no one in the IV lyophilized group. Headache occurred more frequently in the lyophilized groups although the number of

volunteers requiring treatment for headache were similar between the two preparations **(Table 6).**

Table 3Adverse Events MEDI-CP080

Adverse Event	Palivizumab			
	3 mg/kg IM		15 mg/kg IV	
	LIQ (N=12)	LYO (N=12)	LIQ (N=12)	LYO (N=12)
Total Events	22	15	15	18
Volunteers With ≥1 Event	6 (50.0%)	8 (66.7%)	6 (50.0%)	8 (66.7%)
Headache	2 (16.7%)	6 (50.0%)	1 (8.3%)	2 (16.7%)
Dizziness	3 (25.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)
Injection-Site Pain	3 (25.0%)	1 (8.3%)	1 (8.3%)	0 (0.0%)
Rhinitis	0 (0.0%)	0 (0.0%)	2 (16.7%)	3 (25.0%)
Asthenia	1 (8.3%)	1 (8.3%)	2 (16.7%)	0 (0.0%)
Pruritus	0 (0.0%)	0 (0.0%)	2 (16.7%)	2 (16.7%)
Anorexia	2 (16.7%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Pharyngitis	0 (0.0%)	1 (8.3%)	2 (16.7%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	1 (8.3%)	2 (16.7%)
Abdominal pain	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (8.3%)
Chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (16.7%)
Accidental injury	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Dyspnea	1 (8.3%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Allergic reaction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Back pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Pallor	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syncope	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Ecchymosis	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Leukopenia	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Insomnia	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increased cough	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Sinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Hematuria	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
Pyelonephritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)

Serious Adverse Events

There were no serious adverse events among participants in this study.

Study Withdrawals or Deaths

There were no study withdrawals due to adverse events and there were no deaths among participants in this study.

Adverse Events Requiring Treatment:

Five of the 48 subjects in this study developed adverse events requiring treatment **(Table 4).** As previously discussed, treated headaches were infrequent and occurred in similar numbers across the treatment arms. Other treated adverse events were single events.

Table 4 Adverse Events Requiring Medical Intervention

Adverse Event	Palivizumab			
	3 mg/kg IM		15 mg/kg IV	
	LIQ (N=12)	LYO (N=12)	LIQ (N=12)	LYO (N=12)
Total Treated Events	3	1	0	5
Volunteers with ≥1 Treated Event	2 (16.7%)	1 (8.3%)	0 (0.0%)	2 (16.7%)
Headache	1 (8.3%)	1 (8.3%)	0 (0.0%)	1 (8.3%)
Accidental Injury	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Back Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Pain (knee)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
Pyelonephritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)

Abnormal Laboratory Adverse Events:

Two volunteers had increases in toxicity grades for hematology laboratory values from normal at baseline to mild at Study Days 7 and/or 37. Volunteer 468119 in the IM lyophilized group had a normal WBC value at Study Day 0 (4×10^3 cells/μL) and low WBC values at Study Days 7 (2.8×10^3 cells/μL) and 37 (3×10^3 cells/μL). This volunteer also had a low lymphocyte value at Study Day 7 (843 cells/μL, and normal lymphocyte values on Study Days 0 (1284 cells/μL) and 37 (1074 cells/μL). Volunteer 363227 in the IV lyophilized group had a normal WBC on Study Day 0 ($5.3x\ 10^3$ cells/μL), a low WBC value at Study Day 7 (3.5 x 103 cells/μL). No follow-up laboratory testing was performed.

Immunogenicity

Blood samples were collected for measurement of anti-palivizumab antibodies on serum on Study Days 0, 7, 14, 21, 30, and 60 in all treatment groups and one Study Day 37 for the IM groups. A total of 20/48 of all volunteers developed detectable antibodies during the study. **(Table 5).** No member of the IV lyophilized group developed detectable antibodies to palivizumab.2 volunteers in the IM lyophilized group had titers of 1:160 7-14 days after the first injection. These titers decreased subsequently to 1:80 or lower and did not boost following the second injection. One volunteer in the IV liquid group had a titer of 1:160 seven days after the infusion. This titer decreased to <1:10 and remained undetectable throughout the remainder of the study. None of other volunteers in any treatment group had titers greater than 1:80 at any time during the study. The sponsor interpreted the presence of transient low levels of antibodies following the first IM/IV administration as consistent with the development of anti- idiotype antibodies. Due to the long half life of this product, the immunogenicity testing that was done might have been affected by interference from residual palivizumab.

(b) (4)

Conclusions

It was concluded that study MEDI-CP080 raised no concerns about the safety of the liquid palivizumab formulation. The Immunogenicity data was judged to be inconclusive because of the sampling intervals chosen.

STUDY MEDI-CP097

Study Design

Phase II, randomized, double-blind, two-period, cross-over PK study of palivizumab in pediatric patients under 6 months of age at enrollment who had a history of prematurity at ≤ 35 weeks gestation (at high risk of RSV complications) (**Figure 2**).. The dose used in this study, 15 mg/kg IM monthly, is the currently approved dose for administration of palivizumab. Two doses of palivizumab (i.e., one LIQ plus one LYO dose, or one LYO plus one LIQ dose), one on each of Study Days 0 and 30, were considered adequate to compare the two formulations.

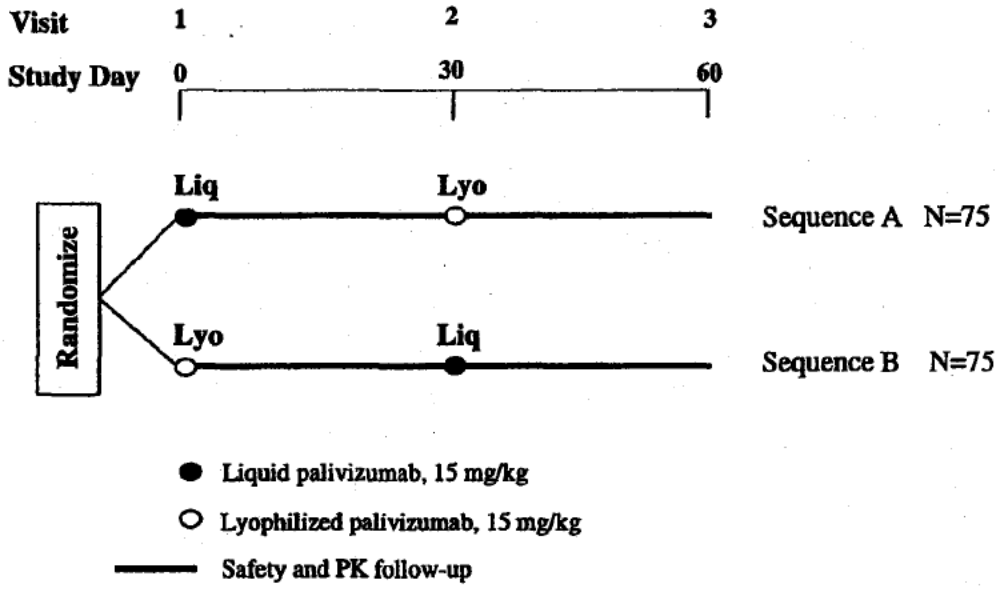
Children were randomized to one of two treatment sequences:

Sequence A: 15 mg/kg LIQ palivizumab IM at Study Day 0 and 15 mg/kg LYO palivizumab IM at Study Day 30

Sequence B: 15 mg/kg LYO palivizumab IM at Study Day 0 and 15 mg/kg LIQ palivizumab IM at Study Day 30

Figure 2 Study Design MEDI-CP097

A flow diagram of the study design is presented below.



Enrollment criteria

The child must have been born at ≤ 35 weeks gestation and have been ≤ 6 months of age at the time of randomization (child must have been randomized on or before their 6-month birthday);

Primary Pharmacokinetic Endpoints

The primary endpoints were the trough concentrations in serum of palivizumab at Study Days 30 and 60.

Secondary Endpoints

Secondary Endpoints were safety assessment including adverse events, vital signs and laboratory data.

Study conduct

Disposition of patients

A total of 153 children were randomized into the study between 01/Nov/02 and 03/Feb/03 at 21 sites in the US. A total of 15 sites randomized 9 children or less, 5 sites randomized between 10 and 16 children and the remaining site randomized 21 children.

Of the 153 children randomized, 152 (99.3%) completed the study through 30 days after the 2nd injection of study drug. For the 1 child who did not complete the study, who was randomized to Sequence B, the child's mother withdrew consent after the 1st injection of study drug as she did not wish her child to have any more injections or blood samples.

Protocol Violations

A total of 6 (4%) patients, 4 randomized to Sequence A and 2 randomized to Sequence B, had eligibility criteria violations **(Table 6):** 5 patients (4 Sequence A, 1 Sequence B) did not meet exclusion criterion #7 (due to laboratory findings outside the specified normal ranges), and 1 patient (Sequence B) did not meet exclusion criterion #2 (due to birth hospitalization >6 weeks duration). All patients with entry violations received both doses of study drug and continued to be followed according to the protocol. These patients were included in all analyses unless otherwise specified.

Table 6 Eligibility Criteria Violations Identified After Randomization

PID	Criterion Not Met	Reason Criterion Not Met
Sequence A		
040003	Exclusion #7[a]	Screening AST (SGOT) of 63 IU/L[c]
073002	Exclusion #7[a]	Screening AST (SGOT) of 94 U/L
073009	Exclusion #7[a]	Screening platelets not obtained due to clumping
187003	Exclusion #7[a]	Screening hemoglobin 7.3 gm/dL
Sequence B		
034007	Exclusion #2[b]	Birth hospitalization was >6 weeks duration (45 days)
187006	Exclusion #7[a]	Screening hemoglobin 8.6 gm/dL

a. Exclusion criterion #7 reads as follows: Any of the following laboratory findings in blood obtained within 7 days prior to study entry: BUN or creatinine >1.5× the upper limit of normal for age; AST (SGOT) or ALT (SGPT) >1.5× the upper limit of normal for age; hemoglobin <9.0 gm/dL; white blood cell count <4,000 cells/mm^3; platelet count <110,000 cells/mm^3.
b. Exclusion criterion #2 reads as follows: Birth hospitalization >6 weeks duration.
c. Site used adult normal range of 0-37 U/L for AST (SGOT).

Analysis Populations

The PK evaluable population **(Table 7)** (N=149; 73 for Sequence A, 76 for Sequence B) included all patients who met the following criteria:

- Received two full doses of study drug;
- Had blood collected at Study Days 30 and 60;
- Had a serum palivizumab concentration <LOQ at Study Day 0;
- Had trough serum concentration values >LOQ at both Study Days 30 and 60.

The protocol evaluable population **(Table 7)** (N=118; 58 for Sequence A, 60 for Sequence B), defined as the primary analysis population, included patients who met the following criteria:

- Were PK evaluable;
- Had blood collection at Study Day 0;
- Had blood collections within the protocol defined windows of Study Day 30 ± 2 days and
  Study Day 60 ± 2 days.

Of the 31 patients included in the PK evaluable population but not in the protocol evaluable population, 2 patients had no blood collection at Study Day 0 and 29 patients had one or both of the Study Day 30 and 60 visits outside the protocol

defined window. These 31 patients were evenly distributed between sequences (15 from Sequence A and 16 from Sequence B).

Four patients (2 for Sequence A, 2 for Sequence B) were not included in either the PK or protocol evaluable populations. In Sequence A, 1 patient had no blood collected after dosing; the other had an undetectable palivizumab level detected after Study Day 30 or 60. In Sequence B, 1 patient did not receive 2 doses; the other had a detectable palivizumab level at Study Day 0 (99.6 μg/mL).

All patients who received any study drug on Study Day 0 were included in the Study Day 0-30 safety analyses, all patients who received any study drug on Study Day 30 were included in the Study Day 30-60 safety analyses, and all patients who received any study drug on either Study Day 0 or 30 were included in the Study Day 0-60 safety analyses. **(Table 7)**

Table 7 Patient Populations for Evaluation

	Seq. A (N=75)	Seq. B (N=78)	Total (N=153)
PK Evaluable Children	73	76	149
Reason not PK Evaluable			
Rec'd <2 doses	0 (0.0%)	1 (1.3%)	1 (0.7%)
Rec'd 2 doses, but no blood coll. at Day 30 or 60	1 (1.3%)	0 (0.0%)	1 (0.7%)
Rec'd 2 doses, had 3 blood coll., but serum conc. >LOQ at Day 0	0 (0.0%)	1 (1.3%)	1 (0.7%)
Rec'd 2 doses, had 3 blood coll., but serum conc. <LOQ at Day 30 or 60	1 (1.3%)	0 (0.0%)	1 (0.7%)
Protocol Evaluable Children	58	60	118
Reason not Protocol Evaluable			
Not PK evaluable	2 (2.7%)	2 (2.6%)	4 (2.6%)
PK evaluable, but no blood coll. at Day 0	1 (1.3%)	1 (1.3%)	2 (1.3%)
PK evaluable, but injection or blood coll. 1 day out of window	9 (12.0%)	10 (12.8%)	19 (12.4%)
PK evaluable, but injection or blood coll. 2 days out of window	5 (6.7%)	4 (5.1%)	9 (5.9%)
PK evaluable, but injection or blood coll. 3 days out of window	0 (0.0%)	1 (1.3%)	1 (0.7%)
PK evaluable, but injection or blood coll. >3 days out of window	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety Populations			
Day 0-30 evaluations	75	78	153
Day 30-60 evaluations	75	77	152

Volunteer Demography:

The gender and racial proportions, ages at entry, gestational ages, and weights of the subjects enrolled into Sequence A and Sequence B were similar **(Table 8).**

Table 8 Baseline Demographics All Randomized Children

	Sequence A (N=75)	Sequence B (N=78)	Total (N=153)
Sex			
Male	42 (56.0%)	39 (50.0%)	81 (52.9%)
Female	33 (44.0%)	39 (50.0%)	72 (47.1%)
Race			
White/Non-Hispanic	36 (48.0%)	39 (50.0%)	75 (49.0%)
Black	26 (34.7%)	18 (23.1%)	44 (28.8%)
Hispanic	9 (12.0%)	14 (17.9%)	23 (15.0%)
Asian	2 (2.7%)	2 (2.6%)	4 (2.6%)
Other	2 (2.7%)	5 (6.4%)	7 (4.6%)
Age at Study Entry (months)			
Mean (SE)	1.6 (0.2)	1.4 (0.2)	1.5 (0.1)
Median	0.9	0.8	0.9
Range	(0.1-5.4)	(0.1-5.3)	(0.1-5.4)
Weight at Study Entry (kg)			
Mean (SE)	3.4 (0.2)	3.4 (0.2)	3.4 (0.1)
Median	2.8	2.8	2.8
Range	(1.7-8.1)	(1.7-8.4)	(1.7-8.4)
Gestational Age (weeks)			
Mean (SE)	33.5 (0.2)	33.3 (0.2)	33.4 (0.1)
Median	34.0	34.0	34.0
Range	(29.0-35.0)	(28.0-35.0)	(28.0-35.0)
Birth Weight (kg)			
Mean (SE)	2.0 (0.0)	2.1 (0.0)	2.1 (0.0)
Median	1.9	2.1	2.0
Range	(1.0-3.1)	(1.2-3.2)	(1.0-3.2)

Adverse Events

Adverse Events by Treatment Group Overall (Study Days 0-60)

The number of children with at least 1 adverse event was similar between the LIQ (n=76 ,50%) and LYO (n=75, 49%-) groups during Study Days 0- 60 **(Table 9)**. The most common adverse events overall were typical for the studied population of children ≤ 6 months of age with a history of prematurity (URI, fever, rhinitis, GI disorder [mostly reflux, 1 formula intolerance], and otitis media). The incidence of individual adverse events was similar between the LIQ and LYO groups during Study Days 0-60, with no events having a difference of at least 4%; the largest difference between the two groups was 3.9%, for nervousness (irritability; 6 [3.9%] LIQ vs. 0 [0.0%] LYO). All 6 instances of nervousness-irritability among subjects receiving the liquid formulation occurred in temporal association with other adverse events. These events included: 3 instances of bilateral otitis media, and one instance each of cough, abdominal gas and teething pain. Of further interest, in the patient listings there were two instances of irritability in patients receiving the lyophilized palivizumab, both in association with fever and upper respiratory tract infection.

Adverse Events by Treatment Group (Study Days 0-30 and 30-60)

The number of children with at least 1 adverse event during each of the Study Day 0-30 and 30-60 study periods was similar between the LIQ and LYO groups **(Table 9).** During the Study Day 0-30 period, there were two events for which the difference between the groups was at least 4%: nervousness (irritability; 4 [5.3%] LIQ vs. 0 [0.0%] LYO) and constipation (3 [4.0%] LIQ vs. 0 [0.0%] LYO). During the Study Day 30-60 period, there were two events for which the difference between the groups was at least 4%: otitis media (5 [6.5%] LIQ vs. 1 [1.3%] LYO) and conjunctivitis (0 [0.0%] UQ vs. 3 [4.0%] LYO). None of the cases of nervousness, constipation, otitis media, or conjunctivitis was considered to be related to study drug.

Adverse Events within Treatment Sequence (Sequence A or Sequence B)

The incidence of children with at least 1 adverse event was higher after the first injection than after the second injection for both Sequence A (40 [53.3%] LIQ vs. 34 [45.3%] LYO) and Sequence B (41 [52.6%] LYO vs. 36 [46.8%] LIQ) **(Table 9).** Within Sequence A, there were two events for which the difference in incidence after the LIQ (1st) and LYO (2nd) injections was at least 4%: nervousness (irritability; 4 [5.3%] LIQ vs. 0 [0.0%] LYO) and constipation (3 [4.0%] LIQ vs. 0 [0.0%] LYO). Within Sequence B, there was one event for which the difference in incidence after the LYO (1st) and LIQ (2nd) injections was at least 4%: oral moniliasis (4 [5.1%] LYO vs. 0 [0.0%] LIQ).

Table 9 Incidence of Adverse Events

	Study Days 0-30		Study Days 30-60		Study Days 0-60	
	LIQ[a] (N=75)	LYO[b] (N=78)	LIQ[b] (N=77)	LYO[a] (N=75)	LIQ (N=152)	LYO (N=153)
Total Events	63	62	50	48	113	110
Children With ≥1 Event	40 (53.3%)	41 (52.6%)	36 (46.8%)	34 (45.3%)	76 (50.0%)	75 (49.0%)
URI	7 (9.3%)	9 (11.5%)	7 (9.1%)	9 (12.0%)	14 (9.2%)	18 (11.8%)
Fever	6 (8.0%)	4 (5.1%)	5 (6.5%)	4 (5.3%)	11 (7.2%)	8 (5.2%)
Rhinitis	4 (5.3%)	6 (7.7%)	5 (6.5%)	5 (6.7%)	9 (5.9%)	11 (7.2%)
Gastrointestinal Disorder	5 (6.7%)	5 (6.4%)	4 (5.2%)	3 (4.0%)	9 (5.9%)	8 (5.2%)
Otitis Media	3 (4.0%)	2 (2.6%)	5 (6.5%)	1 (1.3%)	8 (5.3%)	3 (2.0%)
Rash	4 (5.3%)	4 (5.1%)	3 (3.9%)	3 (4.0%)	7 (4.6%)	7 (4.6%)
Nervousness	4 (5.3%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	6 (3.9%)	0 (0.0%)
Diarrhea	3 (4.0%)	2 (2.6%)	2 (2.6%)	1 (1.3%)	5 (3.3%)	3 (2.0%)
Hernia	2 (2.7%)	3 (3.8%)	2 (2.6%)	1 (1.3%)	4 (2.6%)	4 (2.6%)
Constipation	3 (4.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	4 (2.6%)	0 (0.0%)
Oral Moniliasis	3 (4.0%)	4 (5.1%)	0 (0.0%)	1 (1.3%)	3 (2.0%)	5 (3.3%)
Inj. Site Rxn, Other	0 (0.0%)	0 (0.0%)	3 (3.9%)	2 (2.7%)	3 (2.0%)	2 (1.3%)
Cough	1 (1.3%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	3 (2.0%)	0 (0.0%)
Conjunctivitis	2 (2.7%)	2 (2.6%)	0 (0.0%)	3 (4.0%)	2 (1.3%)	5 (3.3%)
Vomiting	2 (2.7%)	2 (2.6%)	0 (0.0%)	2 (2.7%)	2 (1.3%)	4 (2.6%)
Pain	1 (1.3%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	2 (1.3%)	3 (2.0%)
RSV	1 (1.3%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	2 (1.3%)	3 (2.0%)
Lacrimation Disorder	1 (1.3%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	2 (1.3%)	2 (1.3%)
Flatulence	1 (1.3%)	3 (3.8%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	3 (2.0%)
Fungal Dermatitis	1 (1.3%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	2 (1.3%)
Pneumonia	1 (1.3%)	1 (1.3%)	0 (0.0%)	1 (1.3%)	1 (0.7%)	2 (1.3%)
Acne	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Apnea	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Maculopapular Rash	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (0.7%)	1 (0.7%)
Study Drug Inj. Site Rxn.	0 (0.0%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Abnormal Stools	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Allergic Reaction	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Bradycardia	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Bronchiolitis	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Croup	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Dyspnea	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Vascular Anomaly	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Cardiovascular Disorder	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (1.3%)
Seborrhea	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (1.3%)
Dehydration	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)
Dysphagia	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Eczema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)
Heart Malformation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)
Urinary Tract Infection	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Viral Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)
Wheeze	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)

Note: Events are ordered by incidence for Days 0-60 in the LIQ group.

a. Sequence A

b. Sequence B

Serious Adverse Events:

The incidence of children with at least one serious adverse events was similar between the liquid preparation (5 children [3.3%] each with one serious adverse event) and the lyophilized preparation (4 children [2.6%] with a total of 5 serious adverse events) **(Table 10).** The incidence of children with at least one serious adverse event was also similar after each injection for both Sequence A (3 [4.0%]

LIQ vs 2 [2.7%] LYO) and Sequence B (2 [2.6%] LIQ vs 2 [2.6%] LYO). These events are judged to be attributable to the patients' underlying medical conditions.

Table 10 Serious Adverse Events MEDI-CP097

	Study Days 0-30		Study Days 30-60		Study Days 0-60	
	LIQ[a] (N=75)	LYO[b] (N=78)	LIQ[b] (N=77)	LYO[a] (N=75)	LIQ (N=152)	LYO (N=152)
Total Events	3	3	2	2	5	5
Children With ≥1 Event	3 (4.0%)	2 (2.6%)	2 (2.6%)	2 (2.7%)	5 (3.3%)	4 (2.6%)
RSV	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
Fever	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Gastrointestinal Disorder	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Pneumonia	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Apnea	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Dehydration	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)
Urinary Tract Infection	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (0.7%)

a. Sequence A
b. Sequence B

Study Withdrawals or Deaths

There were no study withdrawals due to adverse events and there were no deaths among participants in this study.

Grade 3 and 4 Adverse Events:

The incidence of patients with reports of at least one Level 3 adverse event during Study Days 0-60 was similar between the LIQ and LYO groups (3 [2.0%] LIQ vs. 4 [2.6%] L YO) and after each injection for Sequence A (2 [2.7%] for both LIQ and LYO) and Sequence B (2 [2.6%] LYO vs. 1 [1.3%] LIQ). Only one Level 4 adverse event was reported (gastroenteritis in patient #042001 after the 2nd injection LIQ, (see **Table 11).** There was no Level 3 adverse event that occurred in more than 1 child in either of the LIQ or LYO groups. An event of Level 3 pneumonia in 1 LYO patient (#207002), not considered a serious adverse event, was judged by the blinded investigator to be possibly related to study drug; prior to this adverse event, the patient had an episode of pneumonia that was serious.

Table 11 Grade 3 and Grade 4 Adverse Events MEDI-CP097

	Study Days 0-60							
	LIQ (N=152)				LYO (N=153)			
	Level 3		Level 4		Level 3		Level 4	
Total Level 3 and 4 Events	4		1		5		0	
Children With ≥1 Level 3 or Level 4 Event	3	(2.0%)	1	(0.7%)	4	(2.6%)	0	(0.0%)
Fever	1	(0.7%)[a,c]	0	(0.0%)	1	(0.7%)[b,c]	0	(0.0%)
Pneumonia	1	(0.7%)[a,c]	0	(0.0%)	1	(0.7%)[b,c]	0	(0.0%)
Diarrhea	1	(0.7%)[a,c]	0	(0.0%)	0	(0.0%)	0	(0.0%)
Gastroenteritis	0	(0.0%)	1	(0.7%)[b,d]	0	(0.0%)	0	(0.0%)
Gastrointestinal Disorder	1	(0.7%)[b,d]	0	(0.0%)	0	(0.0%)	0	(0.0%)
RSV	0	(0.0%)	0	(0.0%)	1	(0.7%)[a,d]	0	(0.0%)
Urinary Tract Infection	0	(0.0%)	0	(0.0%)	1	(0.7%)[a,d]	0	(0.0%)
Vomiting	0	(0.0%)	0	(0.0%)	1	(0.7%)[b,c]	0	(0.0%)

a. Event occurred after the 1st injection of study drug
b. Event occurred after the 2nd injection of study drug
c. Sequence A
d. Sequence B

Adverse Events Requiring Treatment:

Adverse Events requiring medical intervention are summarized in **Table 16**. A total of 52 (34%) of children in the LIQ group and 47 (31%) of patients in the LYO group had at least one adverse event requiring medical intervention during days 0-60 **(Table 12).** The most common adverse events overall during days 0-60 that required medical intervention were URI (5 [3.3%] LIQ versus 11 [7.2%] LYO), gastrointestinal disorder (9 [5.9%] LIQ versus 3 [2.0%] LYO) and otitis media (8 [5.3%] LIQ versus 3 [2.0%] LYO). The nervousness-irritability symptoms were treated with antibiotics for the cases attributable to an underlying infection (otitis media) or analgesics for the non-infectious causes.

Table 12 Adverse Events Requiring Medical Intervention Incidence >1% in LIQ Group

	Study Days 0-30		Study Days 30-60		Study Days 0-60	
	LIQ[a] (N=75)	LYO[b] (N=78)	LIQ[b] (N=77)	LYO[a] (N=75)	LIQ (N=152)	LYO (N=153)
Total Events	40	30	31	25	71	55
Children With ≥1 Event	28 (37.3%)	25(32.1%)	24 (31.2%)	22 (29.3%)	52(34.2%)	47 (30.7%)
Gastrointestinal Disorder	5 (6.7%)	2 (2.6%)	4 (5.2%)	1 (1.3%)	9 (5.9%)	3 (2.0%)
Otitis Media	3 (4.0%)	2 (2.6%)	5 (6.5%)	1 (1.3%)	8 (5.3%)	3 (2.0%)
Nervousness	4 (5.3%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	6 (3.9%)	0 (0.0%)
URI	2 (2.7%)	5 (6.4%)	3 (3.9%)	6 (8.0%)	5 (3.3%)	11 (7.2%)
Rash	2 (2.7%)	2 (2.6%)	3 (3.9%)	2 (2.7%)	5 (3.3%)	4 (2.6%)
Fever	3 (4.0%)	2 (2.6%)	2 (2.6%)	1 (1.3%)	5 (3.3%)	3 (2.0%)
Rhinitis	3 (4.0%)	2 (2.6%)	1 (1.3%)	0 (0.0%)	4 (2.6%)	2 (1.3%)
Oral Moniliasis	3 (4.0%)	4 (5.1%)	0 (0.0%)	1 (1.3%)	3 (2.0%)	5 (3.3%)
Inj. Site Rxn, Other	0 (0.0%)	0 (0.0%)	3 (3.9%)	2 (2.7%)	3 (2.0%)	2 (1.3%)
Diarrhea	2 (2.7%)	0 (0.0%)	1 (1.3%)	1 (1.3%)	3 (2.0%)	1 (0.7%)
Constipation	2 (2.7%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	3 (2.0%)	0 (0.0%)
Conjunctivitis	2 (2.7%)	1 (1.3%)	0 (0.0%)	3 (4.0%)	2 (1.3%)	4 (2.6%)
Pain	1 (1.3%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	2 (1.3%)	3 (2.0%)

Note: Events are ordered by incidence for Days 0-60 in the LIQ group.
a. Sequence A
b. Sequence B

Abnormal Laboratory Adverse Events:

Trough serum palivizumab levels and anti-palivizumab antibody determinations were drawn during the conduct of the study. Serum chemistries and complete hematology were measured at baseline only. Therefore, it is not possible to determine if any abnormal serum chemistries or hematologic abnormalities occurred during the conduct of this study.

Immunogenicity

Blood samples were collected for measurement of anti-palivizumab reactivity at Study Days 0, 30, and 60. A total of 61/75 (81.3%) children for Sequence A and 65/78 (83.3%) children for Sequence B were evaluated. Of these children, there were two with binding activity detected (titer ≥1:10): #187003 (Sequence A) with a titer of 1:40 at Study Day 60 and #050006 (Sequence B) with a titer of 1:10 at Study Day 60. For the 126 subjects for whom anti-palivizumab reactivity was collected, two subjects (1.6%)were positive; this incidence is slightly higher than the 0.7% observed in palivizumab recipients in the registration study (Trial 1) after the 4th injection. The placebo group in Trial 1 had an incidence of anti-palivizumab antibodies of 1.1%.

Conclusions

It was concluded that study MEDI-CP097 raised no concerns about the safety of the liquid palivizumab formulation. The Immunogenicity data was judged to be inconclusive because of the sampling intervals chosen.

D. Adequacy of Safety Testing

Overall, the submitted data were judged to be of sufficient quality and quantity to allow important conclusions to be made about safety and tolerability of liquid palivizumab compared to the licensed lyophilized formulation of palivizumab. Based upon the infrequency and mildness of the abnormal laboratories determined for the adult population, the absence of post exposure serum laboratory testing in the infant population seems unlikely to represent a significant deficiency. Immunogenicity testing in both submitted studies was subject to potential interference from continuing presence of the study products. Additional studies of Immunogenicity of palivizumab should be required.

E. Summarize Critical Safety Findings and Limitations of Data

The critical safety findings of this submission are:

- Overall adverse events, serious adverse events, adverse events requiring treatment appear to be similar in frequency and severity between the two formulations.
- The apparent imbalances of adverse events (e.g. incidence of dizziness, irritability) observed between the liquid and the lyophilized formulations in both adult and pediatric patients on closer examination do not appear to represent significant safety differences between the two formulations.
- Laboratory adverse events following study drug administration were infrequent and mild in the adult volunteer population.
- The incidence of laboratory adverse events following study drug administration in the pediatric population is not determinable in this submission for either formulation due to lack of relevant laboratory testing following product administration. Given the demonstration of comparability of the two formulations and the lack of safety signals in the study, laboratory data were judged to be not necessary.
- Anti-palivizumab antibodies were frequently detected in the adult volunteer but these anti-palivizumab antibodies may represent anti-idiotype antibodies Anti-palivizumab antibodies were detected in two pediatric patients, one in association with each formulation. Interference of residual study product potentially affected Immunogenicity testing in this submission

VIII. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The dosage, regimen and route of administration of the liquid preparation are the same as the licensed lyophilized palivizumab.

IX. USE IN SPECIAL POPULATIONS

A. Critically Evaluate Sponsor's Gender Effects Analyses and Adequacy of Investigation

In study MEDI-CP080, there was a 2:1 preponderance of female subjects. In study MEDI-CP097 which evaluated the product's intended population, the gender ratio was 53:47 male to female. There is no reason to suspect that the female

preponderance among the adults would significantly affect the safety, tolerability or immunogenicity data obtained. The near equality among the second study population should ensure representative data.

B. Critically Evaluate Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Non-Hispanic Caucasians were the predominant population in these studies, 56% in study MEDI-CP080 and 49% in study MEDI-CP097. African Americans were well represented in MEDI-CP097 at 29% as were Hispanics at 15%. Asian subjects were represented at 3% or less in both studies. There is no reason to suspect that palivizumab in Asians would have a different safety or pharmacokinetic profile. All the subjects in study MEDI-CP097 were under 6 months of age.

C. Evaluate Pediatric Program

Although RSV can infect any age group, the intended patient population for this product is under age 2years. Study MEDI-CP097 which provided the data used to support bioequivalence of the two formulations was conducted in children less than 2 years of age. The sponsor has submitted a request for a partial waiver for additional pediatric studies of the liquid formulation on the basis that the indicated population for this product has been studied and usage of this product for children older than 2 years is likely to be infrequent. It is recommended that the waiver be granted.

D. Comment on Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

These data are not required for the purpose of observing the safety and activity of the present submission.

X. CONCLUSIONS AND RECOMMENDATIONS

A. Conclusions

Efficacy: Pharmacokinetic data submitted in this submission support comparability of the liquid and the lyophilized formulations of palivizumab. Changes to the product label which discuss the liquid formulation, its comparability to the lyophilized formulation as well as the mechanisms of administration are warranted.

Safety: Data provided in this submission do not indicate any new safety signals that should be reflected in additions to the adverse events section of the package insert. (b) (4) [redacted]

(b) (4)

B. Recommendations

(b) (4)

Recommendations for Partial Waver of Pediatric Studies
The sponsor has requested a partial waver of pediatric studies for all children outside of the labeled indication i.e. children who are not considered to at high risk of severe RSV disease. Although there is no age specific cut-off which clearly identifies "high risk" from other risk categories, the overwhelming majority of children who receive palivizumab for prophylaxis are under the age of 24months. The reason for this age cut-off is that in children older than 24 months generally have better immune response to RSV and milder disease. The sponsor's contention is that this product is unlikely to be used in substantial numbers in children over the age of 24 months. It is recommended that the request for partial waver of further studies in children older than 24 months be granted.

Recommended Changes to the Label:

(b) (4)

The following Statement should be added to the Adverse Events Section

(b) (4)

(b) (4)

The remainder of the changes proposed by the sponsor to instruct the provider on preparation of the two products are acceptable.

XI. Appendix

Not Applicable.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

CHEMISTRY REVIEW(S)

Memorandum

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

Date: 07/15/04

To: File for STN 103770/5059
Carolyn Renshaw, consult reviewer, TFRB/DMPQ/OC/CDER, HFD-328
Steve Kozlowski, MD Product Reviewer, OPS/OBP/DTP, HFM-555
Vicky Tyson-Medlock, RPM, OND/ODEVI/DRMP, HFM-588

From: Joseph Kutza, Ph.D. facility reviewer, JK 7/21/04
TFRB/DMPQ/OC/CDER, HFD-328

Through: Michael D. Smedley, Branch Chief
TFRB/DMPQ/OC/CDER HFD-328 7/21/04

Applicant: MedImmune, Inc.

Subject: STN: 103770/5059

Product: Synagis®

Filing Action Date: 05/22/04 **Status:** Filed

Action Due Date: **07/23/04**

Review Recommendation: I recommend approval of this supplement for the manufacture of a liquid formulation of Synagis (50 and 100mg single dose vials).

(b) (4)

[redacted]

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Conclusions:

I. I recommend approval of this supplement for the manufacture of a liquid formulation of Synagis (50 and 100 mg single dose vials).

II. I deferred the following sections to the Product Reviewer: acceptability of new formulation, stability, the change in concentration method, and overall product comparability.

cc:

Kutza	HFD-328
Renshaw	HFD-328
Smedley	HFD-328
TFRB Reading Files	HFD-328 (STN:103770/5059)
TFRB Facility Files	HFD-328 (MedImmune, Inc. Gaithersburg, MD and (b) (4), (b) (4)
Hoyt	HFD-320

Revision History:

Prepared by Kutza	07/15/04
Comments by Smedley	07/21/04

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DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Bethesda, MD 20892

PRODUCT REVIEW

Date : 7/21/04

To : File

From : Steven Kozlowski, Acting Director, Division of Monoclonal Antibodies, Chief, Laboratory of Immunobiology - HFM 561

Subject : BLA Supplement to Synagis™ PAS for a liquid formulation.

[redacted], 103770-5036, [redacted] The [redacted] CBE30, 103770-5048, and were deemed acceptable.

This supplement, 103770-5059 addresses the filling and marketing of the liquid formulation.

Therapeutic Agent(s): Synagis™ (Palivizumab), a IgG1,kappa humanized antibody against the A epitope of the Respiratory Syncial Virus (RSV) Fusion protein (F-protein). MedImmune code MEDI-493

Sponsor(s): MedImmune

Clinical Indications(s): Synagis™ (Palivizumab) is indicated 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]

[redacted]

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review Worksheet

Submission Date: 3/19/04, 4/19/04

STN Number: 103770/5059
Product Name: Humanized Mab (MEDI-493, Synagis®) to the F Protein of RSV
Dosage Form: Lyopholized Powder, 50 mg/vial and 100 mg/vial for IM Injection
Indication: Treatment of Pediatric Patients at Risk for RSV Disease
Sponsor: MedImmune, Gaithersburg, MD
Type of Submission: Prior Approval Supplement – Manufacturing Changes for the Production of a Liquid Synagis Formulation (Synagis LQ) at the [redacted] (b) (4).
Related INDs: BB IND-5862, BB IND-6384, BLA 97-1359
Reviewer: Hong Zhao, Ph.D.

Introduction

Synagis (Palivizumab) is approved for prevention of serious lower respiratory tract disease caused by RSV in high-risk infants. A liquid formulation, which differs from the licensed lyophilized formulation in the absence of mannitol, is being introduced to avoid reconstitution step before injection. The formulation compositions are shown below:

Formulation	Palivizumab	Histidine	Glycine	Mannitol	pH
Lyophilized	100 mg/ml	47 mM	3.0 mM	5.6% (w/v)	6.0
Liquid	100 mg/ml	25 mM	1.6 mM	None	6.0

The purpose of this submission is to demonstrate that commercial-scale manufacture of a liquid (LIQ) palivizumab formulation yields a product with biochemical and functional characteristics comparable to the licensed lyophilized (LYO) product. In support of the approval of the LIQ formulation, two studies were conducted to compare the LIQ and the LYO palivizumab in the adult (MEDI-CP080) and the pediatrics (MEDI-CP097), and the results showed that the two formulations are comparable in safety, tolerability, immunogenicity, and pharmacokinetic parameters.

Review of Study MI-CP097

Protocol Title: *A Phase II, Randomized, Double-Blind, Two-Period, Cross-Over Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Liquid Formulation of Palivizumab (MEDI-493, Synagis), a Humanized Respiratory Syncytical Virus Monoclonal Antibody, in Children with a History of Prematurity*

Objectives: The primary objective of this study is to compare the pharmacokinetics (trough concentrations) of the LIQ palivizumab with those of the LYO formulation of palivizumab when administered at 15 mg/kg IM to children ≤6 months of age with a history of prematurity (≤35 weeks of gestation). The secondary objective of this study

was to compare the safety and tolerability between the LIQ and LYO formulations of palivizumab.

Study Conduct: MI-CP097 was a randomized, double blind, multi-center, two-period, cross-over study of two monthly injections of palivizumab during the RSV season. A total of 153 children who met the entry criteria were randomized to receive the treatment as follows:

		LIQ15 mg/kg 100mg/ml (1.2 ml), Lot 02AE001-1	LYO 15 mg/kg 100mg/ml (1 ml), Lot 007942
Sequence A	N=75	Day 0 (Visit 1)	Day 30 (Visit 2)
Sequence B	N=78	Day 30 (Visit 2)	Day 0 (Visit 1)

All patients were scheduled to receive 2 injections and were followed for 30 days after each injection for a total of 60 days. Blood samples were collected at baseline, on Study Day 30 and on Study Day 60 for trough palivizumab serum concentration measurement.

Study Population (Mean±SE (Median)):

Sequence	Sex (M/F)	Race (W/B/H/A/O)	Age (month)	Weight
A (N=75)	42/33	36/26/9/2/2	1.6±0.2 (0.9)	3.4±0.2 (2.8)
B (N=78)	39/39	39/18/14/2/5	1.4±0.2 (0.8)	3.4±0.2 (2.8)
Total (N=153)	81/72	75/44/23/4/7	1.5±0.1 (0.9)	3.4±0.1 (2.8)

Patient Population for Evaluation (This table was taken from the submission):

	Seq. A (N=75)	Seq. B (N=78)	Total (N=153)
PK Evaluable Children	73	76	149
Reason not PK Evaluable			
Rec'd <2 doses	0 (0.0%)	1 (1.3%)	1 (0.7%)
Rec'd 2 doses, but no blood coll. at Day 30 or 60	1 (1.3%)	0 (0.0%)	1 (0.7%)
Rec'd 2 doses, had 3 blood coll., but serum conc. >LOQ at Day 0	0 (0.0%)	1 (1.3%)	1 (0.7%)
Rec'd 2 doses, had 3 blood coll., but serum conc. <LOQ at Day 30 or 60	1 (1.3%)	0 (0.0%)	1 (0.7%)
Protocol Evaluable Children	58	60	118
Reason not Protocol Evaluable			
Not PK evaluable	2 (2.7%)	2 (2.6%)	4 (2.6%)
PK evaluable, but no blood coll. at Day 0	1 (1.3%)	1 (1.3%)	2 (1.3%)
PK evaluable, but injection or blood coll. 1 day out of window	9 (12.0%)	10 (12.8%)	19 (12.4%)
PK evaluable, but injection or blood coll. 2 days out of window	5 (6.7%)	4 (5.1%)	9 (5.9%)
PK evaluable, but injection or blood coll. 3 days out of window	0 (0.0%)	1 (1.3%)	1 (0.7%)
PK evaluable, but injection or blood coll. >3 days out of window	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety Populations			
Day 0-30 evaluations	75	78	153
Day 30-60 evaluations	75	77	152

Assay Method: A validated ELISA that developed by the sponsor and provided linear results in the range of 10 µg/ml (LLOQ) to 750 µg/ml, was used for determination of palivizumab serum concentrations. Patient serum samples and the controls were diluted 10,000-fold in PBS/T-BSA prior to assay.

PK Results: The primary analysis consisted of applying an analysis of variance (ANOVA) appropriate for a 2-way crossover design on the log transformed serum concentration values. This ANOVA was used to assess any potential impact of carryover.

No different carryover effect between the two sequences was found for either the protocol or the PK evaluable populations. As a result, data from both periods were used in the assessment of comparability of the two formulations, and confidence intervals and comparisons were based on within-patient variability.

(b) (4)

Table 1. Trough Serum Palivizumab Concentrations

Sequence	A	B	A	B
	Protocol Evaluable Population		PK Evaluable Population	
Study Day 30	N=58	N=60	N=73	N=76
Mean	55.2	52.0	54.8	51.6
Log_{10} Mean± SD	1.72±0.14	1.70±0.13	1.71±0.15	1.69±0.14
Geometric Mean	52.3	49.7	51.7	49.1
Median (range)	51.2 (26.4-125)	47.5 (16.1-114)	50.7 (26.4-125)	46.8 (16.1-114)
Study Day 60	N=58	N=60	N=73	N=76
Mean	89.9	91.5	88.6	90.0
Log_{10} Mean± SD	1.94±0.13	1.94±0.14	1.93±0.13	1.94±0.13
Geometric Mean	86.2	87.5	84.8	87.2
Median (range)	83.8 (33.9-163)	86.3 (24.5-193)	80.6 (33.9-163)	84.8 (24.5-193)

Synagis has an elimination half-life of approximately 20 days in pediatric patients less than 24 months of age, thus serum concentrations were not expected to return to baseline before the 2nd injection of study drug on Study Day 30. As such, Study Day 60 trough concentrations were expected to be higher than those for Study Day 30.

Table 2. Change in Trough Serum Palivizumab Concentrations from Study Day 30 to Study Day 60 – Protocol Evaluable Population (Adjusted Trough Concentrations)

Sequence	A	B
	Protocol Evaluable Population	
Study Day 60	N=58	N=57[a]
Mean	34.7	42.5
Log_{10} Mean± SD	1.47±0.24	1.58±0.24
Geometric Mean	29.7	37.0
Median (range)	27.3 (7.5-121)	38.2 (7.0-158)

[a]. Three patients, in the Sequence B with decreased troughs from Study Day 30 to Study Day 60 were excluded when calculating the adjusted trough concentration.

Mean change in trough serum palivizumab concentrations in the protocol evaluable population from Study Day 30 to Study Day 60 appeared higher for patients in Sequence B than Sequence A. Troughs for all patients in Sequence A increased from Study Day 30 to Study Day 60. Three patients in Sequence B who had decreased troughs from Study Day 30 to Study Day 60 were excluded when calculating the adjusted trough concentration. No clinical findings (dosing or sampling errors, documented RSV infection, or presence of anti-palivizumab reactivity) were implicated to account for these decreases.

Table 3. Cross ANOVA Results for Trough Serum Palivizumab Concentrations

Tests of Hypotheses for Carryover Effect Using the Type IV MS for Patient (Sequence) as an Error Term						
Population	**Source**	**DF**	**Type IV SS**	**Mean Square**	**F Value**	**P-value**
Protocol Evaluable	Sequence	1	0.00389278	0.00389278	0.15	0.7027
PK Evaluable	Sequence	1	0.00165448	0.00165448	0.06	0.8076

Table 4. 90% Confidence Intervals for Ratios of Least Squares Geometric Means of Trough Serum Palivizumab Concentrations

Population	N	LIQ Geometric Mean	LYO Geometric Mean	Ratio	90% CI
Protocol Evaluable	118	67.64	65.42	1.034	(0.986, 1.084)
PK Evaluable	149	67.13	64.55	1.040	(0.998, 1.083)

Table 5. Ratios of Least Squares Geometric Means of Trough Serum Palivizumab Concentrations

	Population	LIQ N	LIQ Geometric Mean	LYO N	LYO Geometric Mean	Ratio
Study Day 30	Protocol Evaluable	58	52.31	60	49.65	1.053
	PK Evaluable	73	51.67	76	49.14	1.051
Study Day 60 – Study Day 30[a]	Protocol Evaluable	57	37.01	58	29.74	1.244
	PK Evaluable	73	34.17	73	28.55	1.197

a. Three patients in Sequence B with decreased troughs from Study Day 30 to Study Day 60 were excluded when calculating the geometric means.

*The above Tables 3, 4 & 5 were taken from the submission.

Sensitivity Analysis: A post hoc sensitivity analysis was conducted to assess the robustness of the results using subsets of the PK evaluable population. Resampling without replacement and stratified by sequence was used. The results (Table 6) imply that with subsets as small as 15 patients per sequence, the 90% CI falls within the predefined comparability limits at least 98% of the time.

Table 6. Results of Resampling Analysis (taken from the submission)

Number of Patients per Sequence	% of CI within (0.80–1.25)	Range of Lower Bound	Range of Upper Bound
15	97.8	0.771 – 1.145	0.960 – 1.342
20	99.7	0.821 – 1.103	0.990 – 1.267
30	100	0.877 – 1.069	1.018 - 1.205
40	100	0.908 – 1.056	1.017 – 1.162

a. Based on 1000 random resampling replicates per scenario

Immunogenicity: Anti-palivizumab ELISA binding activity was measured at baseline and on Study Days 30 and 60. Among the 124 children evaluated, 2 children (1 in each of Sequence A and Sequence B) had low-titer (≤1:40) anti-palivizumab ELISA binding activity observed at Study Day 60. Since the half-life of palivizumab is around 20 days, the sampling time for anti-palivizumab test is not long enough (>5 $t_{1/2}$) to avoid the assay interference by palivizumab.

Conclusions:

- Pharmacokinetic comparability of the proposed liquid and the marketed lyophilized palivizumab was demonstrated, based on the ratios of least squares geometric means of through serum palivizumab concentrations for the two palivizumab formulations and the 90% confidence intervals for these ratios.
- Proposed liquid palivizumab formulation administered IM at 15 mg/kg, in children ≤6 months of age with a history of prematurity, had a safety and tolerability profile that was similar to that of the marketed lyophilized formulation.

Review of Study MI-CP080

Protocol Title: *A Phase I, Double-Blind, Randomized Study to Evaluate the Safety, Tolerance, and Pharmacokinetics of a Liquid Formulation of MEDI-493 (Palivizumab, Synagis), a Humanized Respiratory Syncytical Virus Monoclonal Antibody, in Healthy Adult Volunteers*

Objectives: The primary objectives of this study were to evaluate the safety and tolerance of liquid (LIQ) and lyophilized (LYO) formulations of palivizumab administered by intramuscular (IM) injection or intravenous (IV) infusion to healthy adult volunteers and to determine the PK of palivizumab at a dose of 15 mg/kg intravenously using LIQ and LYO formulations. The secondary objectives were to determine the PK of palivizumab administered IM at a dose of 3 mg/kg, and to measure anti-palivizumab antibodies following IM injection or IV infusion of palivizumab.

Study Conduct: MI-CP080 was a randomized, double-blind, parallel-group study in healthy adult volunteers (ages of 18-49 years) conducted at two sites.

Group	N	Treatment	Product Lot
1	12	3 mg/kg LIQ palivizumab on Study Days 0 and 30, IM	#205-01-001B
2	12	3 mg/kg LYO palivizumab on Study Days 1 and 30, IM	#007945
3	12	15 mg/kg LIQ palivizumab on Study Day 0, IV	#205-01-001B
4	12	15 mg/kg LYO palivizumab on Study Day 0, IV	#007945

A dose of 15 mg/kg was selected for IV administration, since it is the approved dose level in children for IM administration. Three (3) mg/kg was given IM, because higher doses required a significantly larger administration volume.

Blood samples for palivizumab concentration determination were collected prior to dosing and at 0.25, 0.5, 1, 4, 8, and 12 hours after IM injection or end of IV infusion, and daily through Study Day 5 and on Study Days 7, 14, 21, 30, 37 (IM groups only), and 60. Blood samples for measurement of anti-palivizumab antibody titers in serum were collected on Study Days 0, 7, 14, 21, 30, 37 (IM groups only), and 60.

Assay Method: Serum concentrations of palivizumab and titers of anti-palivizumab antibodies were measured in MedImmune by validated ELISAs, with a linear range between 7.5 μg/ml and 100 μg/ml for palivizumab, and LOQ of <1:10 for antibody titer.

PK Results: PK parameters for LIQ and LYO palivizumab administered at 3 mg/kg and IV at 15 mg/kg are summarized in Table 1. For each route of administration, the mean serum concentration of palivizumab at Study Day 30 (C_{trough}), mean AUC, C_{max}, T_{max}, $t_{1/2}$, V_d and CL_t were similar for both formulations of palivizumab.

Table 1. Summary of Palivizumab PK Parameters (Mean±SE)

Parameter	3mg/kg IM		15 mg/kg IV	
	LIQ (n=12)	LYO (n=12)	LIQ (n=12)	LYO (n=12)
C_{trough} (μg/ml)	9.7±1.8	8.8±1.8	75.4±8.1	69.8±4.4
AUC_{0-30} (μg.day/ml)	569±56	511±44	4240±335	4390±229
AUC_{0-inf} (μg.day/ml)	890±112	844±120	6673±749	6310±414
C_{max} (μg/ml)	32.6±2.4	29.6±2.8	502±36	585±32
T_{max} (day)	3.06±0.26	3.89±0.59	0.16±0.05	0.09±0.05
$T_{1/2}$ day)	19.8±3.4	20.1±3.3	20.6±2.2	18.3±1.9
V_d (ml/kg)	168±42	169±25	107±9.8	94±11
CL_t (L/day)	0.43±0.05	0.45±0.04	0.26±0.02	0.25±0.02
CL_t (ml/day/kg)	5.83±0.53	6.33±0.50	3.79±0.30	3.51±0.18

Immunogenicity: Forty-two percent (42%) of study subjects had detectable anti-palivizumab antibodies (20/48) but no subjects in the 15 mg/kg LYO IV group developed detectable antibodies to palivizumab. None of the subjects had titers greater than 1:80 at any time during the study except that one subject in each of the LYO IM group and the LIQ IV group had titers of 1:160 7 to 14 days after the first injection. Their titers decreased subsequently to 1:80 or lower throughout the study. Since the half-life of palivizumab is around 20 days, the sampling time for anti-palivizumab antibodies test is

not long enough (>5 $t_{1/2}$), especially for the IM group, to avoid the assay interference by palivizumab.

Conclusions:

- LIQ palivizumab was safe and tolerated in healthy adults when administered by the IM route at 3 mg/kg or by the IV route at 15 mg/kg.
- The safety, pharmacokinetics, and immunogenicity profiles of LIQ palivizumab were similar to those of LYO palivizumab.

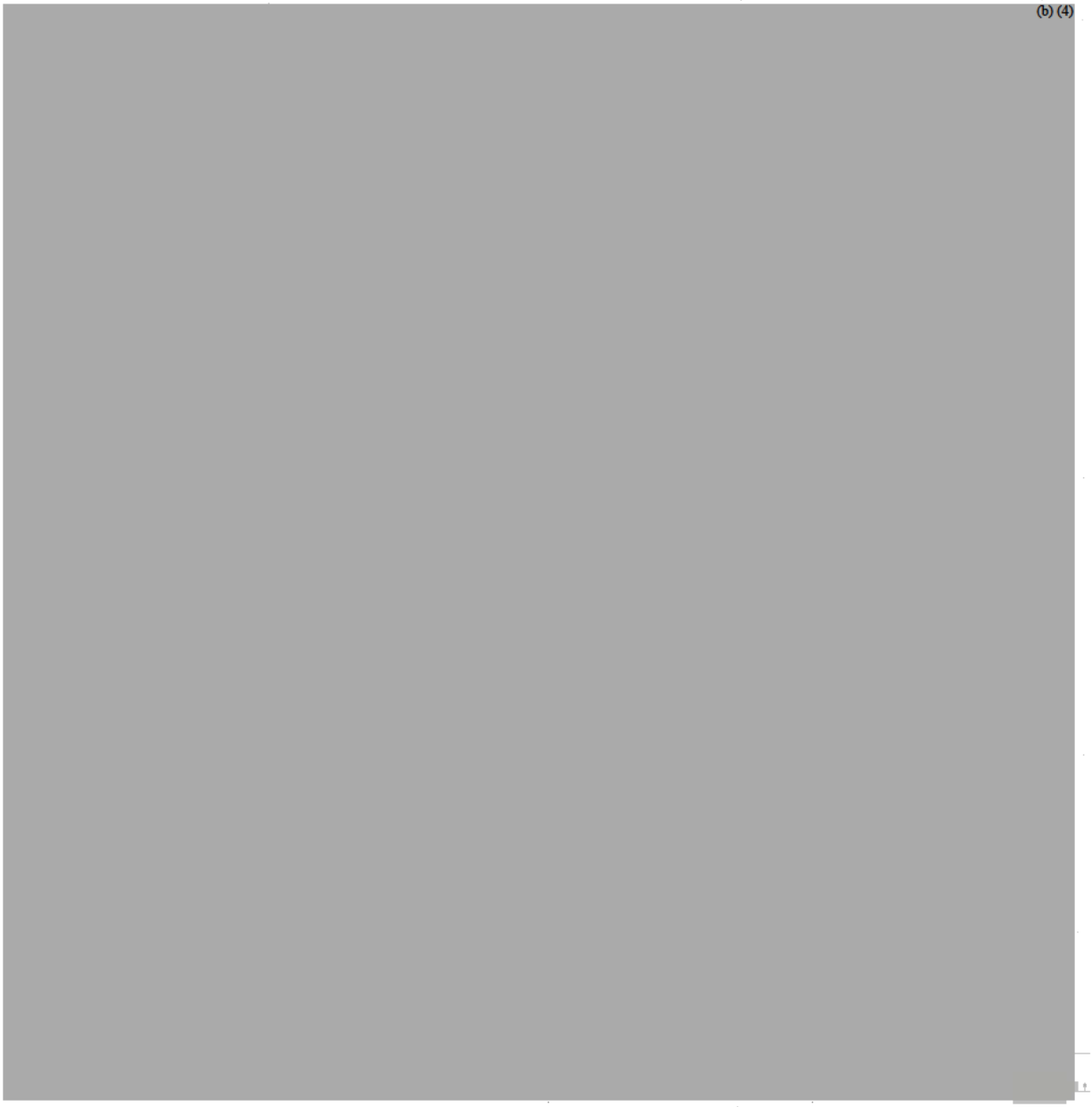
(b) (4)

[redacted]

Sponsor Proposed Labeling Changes (underlined) **and Reviewer's Recommendations** (in red and italic)

(b) (4)

[redacted]



Recommendation

Since the comparability between the proposed liquid palivizumab formulation and the marketed lyophilized formulation has been demonstrated in systemic exposure (trough palivizumab serum concentrations), tolerability and safety in the targeted pediatric patients, the approval of the proposed liquid palivizumab formulation can be granted.

Hong Zhao, Ph.D. 7/14/04
Clinical Pharmacology Reviewer

Martin David Green, Ph.D. 7/14/04
~~Branch Chief~~, Clinical Pharmacology and Toxicology
Supervisor,

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

OTHER REVIEW(S)

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 103770/5059

☐ Initial Assignment
☒ Change

Applicant: MedImmune, Incorporated

Product: Palivizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
V. Tyson-Medlock	Reg. Project Manager	Admin/Regulatory	Kay Schneider	4-28-04
	Reviewer	Admin/Regulatory		
	Reviewer	Product*		
	Reviewer	Product*		
	Reviewer	Product		
	Reviewer	Clinical		
	Reviewer	Clinical		
Hong Zhao	Reviewer	Clinical Pharmacology	Martin Green	6-18-04
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
	Reviewer	Labeling		
		Other		

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

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

Submitted by RPM:

V. Tyson-Medlock — Name Printed
V. Tyson-Medlock — Signature
7-16-04 — Date

Memo entered in RMS by: _____ Date: _____ QC by: LB Date: 7-27-04

S:\DARP\FORMS\BLA Committee Assignment.doc
Final: 4/16/02; 4/18/02;6/14/02;7/14/03

First Committee Meeting: STN 103770/5059

From: Jeanne M. Delasko, RN, MS
Regulatory Project Manager
ODE VI/DRMP, HFM-588

Date: April 6, 2004

Location: WOC II, 6056

Time: 11:42 a.m.

Product: Palivizumab

Applicant: MedImmune, Inc.

Participants: Jeanne Delasko; William Tauber; Joseph Kutza; Carolyn Renshaw; Steve Kozlowski; Dave Green

The following notification was sent email to the committee members:

MedImmune submitted a PAS, standard 4 month review, "to provide for a liquid formulation of Palivizumab in 50mg and 100mg single-use vials." This PAS is submitted as hard copy (5 volumes). It contains CMC and Establishment information and an updated package insert. I have two copies available to route. On 3/26/04, I requested the company submit 3 extra copies. For initial processing, a copy will be routed to Joe Kutza and Steve Kozlowski. When the 3 extra copies are rec'd, they will be routed to Carolyn, Dave and Bill.

The committee members are:
RPM - Jeanne Delasko
Chair - Bill Tauber (Since this is a formulation change and has changes to the PI, it will require sign off by the clinical DD.)
CMC - Steve Kozlowski
P/T - Dave Green
Facilities - Joe Kutza
Consult - Carolyn Renshaw

Enclosed is the filing review memo that each committee member must complete for their discipline and return to me by 5/7/04. The filing action is 5/21/04. The first action due is 7/23/04. Call me if you have any questions 594-5469. Thanks.

ODE VI:DRMP:JMDelasko:4/6/04
(S:/Delasko/MedImmune[Palivizumab]/103770.5059/FirstComMeeting)

BLA/NDA/PMA
Review Committee Assignment Memorandum

☒ Initial Assignment
☐ Change

STN: 103770/5059

Applicant: MedImmune, Inc.

Product: Palivizumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Jeanne M. Delasko	Reg. Project Manager	Admin/Regulatory	Kay Schneider	3-25-04
	Reviewer	Admin/Regulatory		
Steven Kozlowski	Reviewer	Product*	Steven Kozlowski	3-25-04
	Reviewer	Product*		
	Reviewer	Product		
William Tauber	[redacted] Chairperson	Clinical	Louis Marzella	3-25-04
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
Dave Green	Reviewer	Pharm/Tox	Dave Green	3-29-04
	Reviewer	Biostatistics		
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
Joe Kutza	Reviewer	CMC, Facility*	Michael Smedley	3-25-04
		Labeling		
Carolyn Renshaw	Consult	Other	Michael Smedley	3-25-04

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

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

Submitted by RPM:

Jeanne M. Delasko (Name Printed) Jeanne M. Delasko (Signature) 4-6-04 (Date)

Memo entered in RMS by: DCS Date: 4/7/04 QC by: KB Date: 4/8/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

APR 07 2004

MedImmune, Incorporated
Attention: Peter Patriarca, M.D.
Vice President, Regulatory Affairs
One MedImmune Way
Gaithersburg, M.D. 20898

Dear Dr. Patriarca:

SUBMISSION TRACKING NUMBER (STN) BL 103770/5059 has been assigned to your recent supplement to your biologics license application for Palivizumab received on March 23, 2004, to provide for a liquid formulation of Palivizumab in 50mg and 100mg single-dose vials.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Unless we notify you within 60 days of the receipt date that the supplement is not sufficiently complete to permit substantive review, this supplement will be considered filed.

All future correspondence or supportive data relating to this supplemental application should bear the above STN. 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/cder/biologics/default.htm. Until further notice, however, all correspondence 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 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.

If you have any questions, please contact the Regulatory Project Manager, Jeanne Delasko, at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

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: 103770/5059 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 _____ Committee Recommendation (circle one): (File) RTF

RPM: [signature] 5704
(signature/date)

Attachments:

- [X] Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - [X] Part A – RPM
  - [X] Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - [X] Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - [X] Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers M. Tauber _____ _____
- [ ] Memo of Filing Meeting

STN 103770/5059 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)	NA
Comprehensive Table of Contents	(Y) N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y (N)	
User Fee payment received	Y (N)	
Financial certification &/or disclosure information	Y (N)	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y (N)	
Pediatric rule: study, waiver, or deferral	Y (N)	
Labeling:	Y N	
☐ PI –non-annotated	Y N	
☒ PI –annotated	(Y) N	
☒ PI (electronic) – dise	(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)	

STN 103770/5059 Product Palivizumab

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

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? NO

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

- Name:
- Dates:

Recommendation (circle one): File RTF

RPM Signature: [signature] Branch Chief concurrence: Schneider 6-16-04

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	N/A.
▫ 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)	N/A
▫ Case report forms	Y (N)	N/A
▫ Individual patient listings (indexed by study)	Y (N)	
○ 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	
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	
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 electonic datasets complete & usable?	BiMo sites identified?
M1-CP080	(Y) N	Y N (NR)	Y N	Y N (NR)
M1-CP097	(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?

No.

Is an Advisory Committee needed?

No.

Recommendation (circle one): File RTF

Reviewer: [signature] Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date) 21 MAY 04

Concurrence:

Branch Chief: [signature] Division. Director: _____
(signature/ date) May 21 2004 (signature/ date)

Part B – Product/CMC/Facility Reviewer(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum of Filing Review

STN:	103770/5059
Applicant:	MedImmune
Product:	Synagis
Short Summary:	Liquid formulation of palivizumab in 50mg & 100mg single dose vials
Reviewer:	Joseph Kufta
Office/Division:	OBP/DMA

I have conducted a filing review of the above referenced BLA supplement to determine whether it is sufficiently complete to permit a complete review.

Brief description of the change:

The following was submitted in support of the change (check all that apply):

✓	A detailed description of the proposed change
✓	Identification of the product(s) involved
✓	A description of the manufacturing site(s) or area(s) affected
✓	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
✓	The data derived from such studies
✓	Relevant validation protocols and data
✓	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

Recommendation:

✓	I recommend that this supplement be filed.
	I recommend that this supplement be refused for filing for the reasons stated above.

Reviewer: [signature] 7/21/04 Type (circle one): Product (Chair) (Facility (DMPQ))
(signature / date)

Concurrence:
Branch/Lab Chief: [signature] Division Director: _____
(signature / date) (signature / date)
7/21/04

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	N/A, clinical
▫ Clinical Safety	Y	N	N/A, clinical
▫ 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	N/A, clinical
▫ 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	N/A, clinical
◻ 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	N/A, clinical
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	N/A, clinical
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y N	N/A. clinical
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A, clinical
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	N/A, clinical
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	N/A, clinical
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A, clinical
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	N/A. clinical
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	N/A, clinical

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	N/A, clinical
adequate characterization of product specificity or mode of action	Y N	N/A
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	N/A,
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	N/A, clinical

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
MI-CP097 (comparability study)	(Y) N	Y N NR	(Y) N	Y N NR
MI-CP080 (c study)	(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).

There are no filing issues with Clinical Pharmacology part of the submission.

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

Is an Advisory Committee needed?

No.

Recommendation (circle one): (File) RTF

Reviewer: Hong Zhao 3/30/04 Type (circle one): Clinical (Clin/Pharm) Statistical
(signature/ date)

Concurrence:

~~Branch Chief~~ Supervisor: for MDG (signature/ date) Division. Director: (signature/ date) 7/2/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103770/S-5059

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

TELECOMMUNICATION

Date : 7/20/04

To : File

From : Steven Kozlowski, Acting Director, Division of Monoclonal Antibodies, Chief, Laboratory of Immunobiology, HFM 564

Subject : 103770-5059

THERAPEUTIC AGENT(S): Synagis®

SPONSOR(S): MedImmune

SPONSOR REPESENTATIVE(S): [redacted] (b) (6)

FDA REPRESENTATIVE(S): Steven Kozlowski

CALL INITIATOR: FDA

DATE & TIME: 7/15/04 ~3 PM

[redacted] (b) (4)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

TELECOMMUNICATION

Date : 7/20/04

To : File

From : Steven Kozlowski, Acting Director, Division of Monoclonal Antibodies, Chief, Laboratory of Immunobiology, HFM 564

Subject : 103770-5059

THERAPEUTIC AGENT(S): Synagis®

SPONSOR(S): MedImmune

SPONSOR REPESENTATIVE(S): (b)(6)

FDA REPRESENTATIVE(S): Steven Kozlowski

CALL INITIATOR: Sponsor

DATE & TIME: 7/20/04 8:50 AM

(b)(4)

1 Page(s) 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 Biologics Evaluation and Research

Memorandum

Meeting or Teleconference Date: July 19, 2004 **Time: 11:30 a.m.**

Sponsor: Med Immune

Product: Palivizumab, Synagis

STN 103770/5059-to provide Synagis in a liquid formulation, 50 and 100 mg single-dose vials

Proposed Use: RSV

Teleconference Purpose: Package Label Review

DISCUSSION:

I called MedImmune and informed (b) (6) that the revised package labels submitted are acceptable.

FDA Participants:

Victoria Tyson-Medlock

Sponsor Participants:

(b) (6)

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

Memorandum

Meeting or Teleconference Date: July 14, 2004 **Time: 11:30 a.m.**

Sponsor: Med Immune

Product: Palivizumab, Synagis

STN 103770/5059-to provide Synagis in a liquid formulation, 50 and 100 mg single-dose vials

Proposed Use: RSV

Teleconference Purpose: Label Review and Information request

DISCUSSION:

Dr. William Tauber and I called Med Immune and left a message with (b) (6) requesting financial disclosure information. This was the second request for this information.

FDA Participants:

William Tauber and Victoria Tyson-Medlock

Sponsor Participants:

(b) (6)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

TELECOMMUNICATION

Date : 7/14/04

To : File

From : Steven Kozlowski, Acting Director, Division of Monoclonal Antibodies, Chief, Laboratory of Immunobiology, HFM 564

Subject : 103770-5059

THERAPEUTIC AGENT(S): Synagis®

SPONSOR(S): MedImmune

SPONSOR REPESENTATIVE(S): Peter Patriarcha (b) (6)

FDA REPRESENTATIVE(S): Steven Kozlowski

CALL INITIATOR: FDA

DATE & TIME: 7/6/04 3:40 AM

CONTENT:

(b) (4)


(b) (4)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

TELECOMMUNICATION

Date : 7/14/04

To : File

From : Steven Kozlowski, Acting Director, Division of Monoclonal Antibodies, Chief, Laboratory of Immunobiology, HFM 564

Subject : 103770-5059

THERAPEUTIC AGENT(S): Synagis®

SPONSOR(S): MedImmune

SPONSOR REPESENTATIVE(S): Peter Patriarcha

FDA REPRESENTATIVE(S): Steven Kozlowski

CALL INITIATOR: Sponsor

DATE & TIME: 7/14/04 8:40 AM

CONTENT:

Medimmune called in response to a message left about 8AM by Steven Kozlowski. The following issues were brought up:

(b) (4)

[redacted]

(b) (4)

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103770/5059

MAY 21 2004

MedImmune, Incorporated
Attention: Peter Patriarca, M.D.
Vice President, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20898

Dear Dr. Patriarca:

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

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

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/cder/biologics/default.htm. Until further notice, however, all correspondence 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

If you have any questions, please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research