MEMORANDUM

Date: May 5, 2010

To: Antiviral Drug Products Advisory Committee Members and Guests

From: Motavizumab Review Team

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Subject: Background Package for BLA 125283 motavizumab

1. SUMMARY OF REGULATORY ISSUES AND PURPOSE OF MEETING

This briefing document provides background information and the FDA perspective on the Biologics Licensing Application (BLA) submitted by MedImmune for motavizumab, a monoclonal antibody intended for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. The information presented in this document represents the preliminary findings and opinions of the primary reviewers from each discipline based on their review of the submitted material. The material included in this briefing document and other material presented by the applicant will be the subject of a meeting of the Antiviral Drug Products Advisory Committee to be held on June 2, 2010.

Motavizumab (also known as MEDI-524) is a recombinant humanized monoclonal IgG1 κ antibody that binds to the A epitope of the respiratory syncytial virus (RSV) fusion (F) protein. Motavizumab was developed by affinity maturation with 13 amino acid substitutions relative to its parent compound palivizumab (Synagis®). Motavizumab is made in NSO cells using recombinant DNA technology; this process was developed by the applicant of this BLA, MedImmune, who also distributes palivizumab.

This Biologics Licensing Application (BLA) was submitted in accordance with regulations and guidance. Motavizumab is intended to provide prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were studied in infants with a history of premature birth (≤ 35 weeks gestational age), children with chronic lung disease (CLD) of prematurity, and children with hemodynamically significant congenital heart disease (CHD).

FDA analyses of the safety and efficacy data submitted in the BLA raise questions about the product's safety and efficacy. This BLA relies primarily on two Phase 3 trials and one Phase 2 trial to support licensing of motavizumab as briefly described below. In all three studies, the primary efficacy endpoint is prevention of respiratory hospitalizations due to RSV.

MI-CP110: a randomized, double-blind, active comparator, non-inferiority trial enrolling 6635 subjects compared motavizumab to palivizumab for prophylaxis of severe RSV disease in prematurely born infants ≤ 35 weeks gestational age (GA) at birth and ≤ 6 months of age at randomization and infants plus toddlers less than 24 months of age with chronic lung disease of prematurity.

MI-CP117, a randomized, double-blind, placebo-controlled trial enrolling 1410 subjects was designed to determine if MEDI-524 compared to placebo would result in reduction of RSV hospitalizations in otherwise healthy Navajo and White Mountain Apache (WMA) infants during their first RSV season.

MI-CP124, a Phase 2, randomized, double-blind, active comparator, safety, tolerability, pharmacokinetics and immunogenicity trial enrolling 1236 subjects compared motavizumab to palivizumab for prophylaxis of severe RSV disease in children with hemodynamically significant congenital heart disease

The Advisory Committee will be asked to review and discuss issues related to the safety and efficacy of motavizumab as well as the risk/benefit assessment of the drug.

Issues for the Advisory Committee

1) We have concerns that motavizumab may have more of an affect on the accuracy of some local RSV testing assays compared to palivizumab. Therefore, results of local testing may have potentially skewed respiratory admissions and biased the treatment effect in favor of motavizumab in the two phase 3 trials.

2) Achieving noninferiority in trial MI-CP110 was driven by results obtained from the 9% of subjects enrolled in southern hemisphere sites.

3) Motavizumab has three times as many non-fatal hypersensitivity adverse events including urticaria as palivizumab with an overall rate of about 1%. Also in MI-CP110 skin/hypersensitivity reactions were the predominant cause of adverse event discontinuations for motavizumab patients occurring in 9 of 13 such discontinuations. In contrast, none of the 10 discontinuations in CP-110 palivizumab's arm were due to skin/hypersensitivity reactions. Given motavizumab has a higher degree of hypersensitivity than the approved product palivizumab with some questions about motavizumab's efficacy, does the risk-benefit assessment favor the licensure of motavizumab?

2. SUMMARY OF CLINICAL DEVELOPMENT

The clinical development program for motavizumab was modeled after the palivizumab development program with the goal of providing an improved product for RSV immunoprophylaxis initially in premature infants and children with chronic lung disease of

prematurity and subsequently in children with hemodynamically significant congenital heart disease.
MedImmune carried out five Phase 1 and 2 studies as part of the development program for motavizumab (MI-CP101, 104, 106, 118, and 127 –see Table B1 below). MedImmune began their "pivotal" Phase 3 study CP-110 prior to the Agency's review of their protocol. MedImmune decided to exclude patients with congenital heart disease from MI-CP110 choosing instead to study this population in a subsequent Phase 2 safety trial MI-CP124.

Initial review of data from MI-CP110 indicated that the RSV hospitalization rates for both study arms were lower than anticipated. The RSV hospitalization rates in the palivizumab and motavizumab arms were 1.9% and 1.4% respectively in the all randomized population (ITT). This compares to a hospitalization rate of 4.8% in the palivizumab arm of MI-CP018, the original palivizumab registrational trial conducted during the years 1996-1997. The review of data also indicated important population differences between MI-CP110 and MI-CP018. MI-CP110 had: lower proportion of patients with CLD, fewer patients of less than 32 weeks gestational age, fewer non-Caucasian minority patients and was largely done outside North America compared to MI-CP018. These findings complicated the interpretation of non-inferiority in MI-CP110. Therefore, data from study MI-CP117, a placebo controlled trial of motavizumab in Native American full term otherwise healthy infants was requested by the Agency to provide additional efficacy support for MI-CP110. The population of CP-117 is significantly different from CP-110 and consists of healthy full term Native American infants previously recognized to be at higher risk of serious RSV disease as compared to other healthy full term infants.

Table B-1 Clinical Development Summary Motavizumab

CLINICAL DEVELOPMENT SUMMARY				
Study Number	Study Title	Phase	Participating Countries	Subjects Randomized
110	A Pivotal Phase 3 Study of MEDI-524 (Numax™), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prophylaxis of Serious RSV Disease in High-Risk Children	3	International 24 countries both Northern and Southern Hemispheres	6635
117	A Phase 3 Study of MEDI-524 (Motavizumab), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prevention of RSV Disease Among Native American Infants in the Southwestern United States	3	Southwestern USA	1410
124	A Phase 2, A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody against Respiratory Syncytial Virus (RSV), in Children with Hemodynamically Significant Congenital Heart Disease	2	International 16 countries (Northern Hemisphere only)	1236

127	A Phase 2, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of Motavizumab (MEDI-524), a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), and Palivizumab When Administered in the Same Season	2	7 Chilean, 6 Australian and 5 New Zealand sites	260
118	A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), after Dosing for a Second Season in Children who Previously Received MEDI-524 in Protocol MI-CP104	1/2	6 South American Sites	136
106	A Phase 1, Randomized, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of a Single Intravenous Dose of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody to Respiratory Syncytial Virus (RSV), in Otherwise Healthy Children Hospitalized with RSV Infection	1	2 sites, one in USA and the other in Chile	30
104	A Phase 1/2, Open-label, Repeat-Dose, Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity, and Pharmacokinetics of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody Against Respiratory Syncytial Virus (RSV), in Children at Risk for Serious RSV Disease	1/2	16 sites, 9 in the USA and 7 in South America	217
101	Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI-524 (NUMAX ™), a Humanized Enhanced Potency Monoclonal Antibody against Respiratory Syncytial Virus (RSV), in Healthy Adults	1	1 site USA	30

3. SUMMARY OF EFFICACY DATA

Dose Selection: The doses of motavizumab and palivizumab are both 15mg/kg IM. During development other doses of motavizumab including 3mg/kg were evaluated and the 15mg/kg dose yielded pharmacokinetics most similar to palivizumab.

Summary of Study Designs

Phase 3 Studies

MI-CP110

Title: "A Pivotal Phase 3 Study of MEDI-524 (Rezield™), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prophylaxis of Serious RSV Disease in High-Risk Children"

Study Design: Phase 3, randomized, double-blind, palivizumab-controlled, multi-center, multinational trial. Premature infants (gestational age ≤ 35 weeks) less than 6 months of age at enrollment and children ≤ 2 years with documented chronic lung disease (CLD) both at increased risk of serious RSV infection were randomized in a 1:1 ratio to receive motavizumab or palivizumab at 15 mg/kg by IM injection every 30 days for a total of 5 injections. Randomization was blocked by study site and stratified according to the presence/absence of chronic lung disease (CLD) of prematurity requiring medical intervention/management.
The trial was designed to provide passive immunoprophylaxis for 150 days or an average RSV season. The endpoints of documented RSV hospitalization, documented outpatient RSV lower respiratory tract infection represent failures of immunoprophylaxis to prevent serious RSV infection. The other secondary endpoints of incidence of episodes of otitis media, and all lower respiratory tract infections as well as the use of antibiotics in their treatment provide indirect evidence of efficacy owing to the prominence RSV has in causing these illnesses in this patient population.

Methodology: All patients were evaluated just prior to each injection of study drug with a final post dosing follow-up at Study Day 150. All clinical events were captured. The nasal secretions of any patient hospitalized with a compatible respiratory illness or who developed a worsening of respiratory symptoms during a hospitalization were collected and submitted for RSV testing in a central laboratory. Respiratory secretions for RSV testing were to be collected within 2 days of hospital admission, or as soon as possible thereafter. All positive RSV test results were counted if they occurred in a nasal sample collected within ± 5 days of the admission/deterioration date or from samples collected within 11 days after the admission/deterioration if the study site physician designated that the sample was collected for the event. Patients who died during the trial who had not already had nasal specimens tested in this way had clinical specimens submitted for culture if RSV was considered a possible cause of death. Documentation of RSV as causative of the respiratory hospitalization was made through submission of nasal secretions of hospitalized patients for central real-time reverse-transcriptase polymerase chain reaction (real-time RT-PCR) RSV diagnostic test for RSV A and RSV B. The decisions to hospitalize or provide outpatient management of individual patients were made locally, possibly by the site investigator but more often by the patient's primary care or emergency room provider. The sponsor allowed such clinical decisions to be made in accordance with local standard of care to include the use of locally available RSV diagnostic assays. The use and results of local RSV testing were not systematically collected by the sponsor.

Patients at all sites participated in the primary endpoint of hospitalizations. The secondary endpoints of all medically-attended lower respiratory tract infections(MALRI) (without regard to RSV status), medically-attended otitis media and antibiotic use for otitis media were also collected on the entire population. The secondary endpoint of medically attended lower respiratory tract infections (MALRI) caused by RSV was performed at a subset of study sites. At these self-selected sites, the nasal secretions of all patients presenting with symptoms of lower respiratory tract infection were submitted in the same manner as they were for hospitalizations.

Dates Conducted: The trial was conducted during 2 consecutive northern hemisphere seasons with an intervening RSV season in the southern hemisphere enrolling a total of 6635 patients at a total of 347 sites in 24 countries. Each child only participated during a single RSV season.

Study MI-CP117

Title: "A Phase 3 Study of MEDI-524 (Numax TM), an Enhanced Potency Humanized Respiratory Syncytial Virus (RSV) Monoclonal Antibody, for the Prevention of RSV Disease among Navajo and White Mountain Apache Infants

Purpose: Original purpose was to address the question if passive immunoprophylaxis might benefit full term Native American infants who for unknown reasons are known to be at increased risk of serious RSV infection.(see publication: Bockova J, O'Brien KL, Oski J, Croll J, Reid R, Weatherholtz RC, Santosham M, Karron RA. Respiratory syncytial virus infection in Navajo and White Mountain Apache children. Pediatrics. 2002 Aug;110.

Study Design:
MI-CP117 is a Phase 3, randomized, double-blind, placebo-controlled trial designed to determine if MEDI-524 compared to placebo will result in clinical efficacy in the reduction of RSV hospitalization in otherwise healthy Navajo and White Mountain Apache (WMA) infants less than 6 months of age at enrollment during their first RSV season. In this study, otherwise healthy full term Native American Infants would be randomized 2:1 to receive 15 mg/kg of motavizumab or placebo IM monthly for a planned 5 injections. Randomization was blocked by sites. The entire trial duration was for 150 days during which time the incidence of RSV hospitalizations, outpatient lower respiratory infections caused by RSV, episodes of otitis media and adverse events would be compared between the two treatment arms.

Methodology: All patients were evaluated just prior to each injection of study drug with a final post dosing follow-up at Study Day 150. Patients who died during the trial who had not already had nasal specimens tested in this way had clinical specimens submitted for culture if RSV was considered a possible cause of death. Documentation of RSV as cause of the respiratory hospitalization was made through submission of nasal secretions of hospitalized patients for central real-time reverse-transcriptase polymerase chain reaction (real-time RT-PCR) RSV diagnostic test for RSV A and RSV B. The decisions to hospitalize or provide outpatient management of individual patients were made locally, possibly by the site investigator but more often by the patient's primary care or emergency room provider. The sponsor allowed such clinical decisions to be made in accordance with local standard of care to include the use of locally available RSV diagnostic assays. The use and results of local RSV testing were not systematically collected by the sponsor.

Dates Conducted: November 15, 2004 through May 30, 2007

Endpoints:

Primary endpoint:

- Comparison of incidence of RSV hospitalization from study day 0 through study day 150 of the child's first RSV season between study arms. Also included were deaths caused by RSV. Respiratory secretions for RSV testing were to be collected within 3 days of hospital admission or as soon as possible thereafter. All positive RSV test results were counted if they occurred in a nasal sample collected within 11 days after the admission/deterioration if the study site physician designated that the sample was collected for the event.

Secondary endpoints:

- Comparison of RSV-Specific Medically Attended Outpatient Lower Respiratory Tract Infection between study arms during the time period above. Respiratory secretions for RSV testing were to be collected within 3 days of an outpatient medically attended lower respiratory illness or as soon as possible thereafter. All positive RSV test results were counted if they occurred in a nasal sample collected within ± 5days of the outpatient date or within 11 days after the outpatient visit if the PI designated that the sample was collected for the event.
- Comparison of the incidence of otitis media during the study period, summarized by numbers and percentages of patients who had 0.1, 2, and ≥ 3 episodes
- Immunogenicity- summarized at baseline and at study day 120 or at any time by determining the number and percentage of patients who developed detectable anti-motavizumab antibodies ($\geq$ 1:10).

Phase 2 Study

MI-CP-124

Title: A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Immunogenicity of MEDI-524, a Humanized Enhanced Potency Monoclonal Antibody against Respiratory Syncytial Virus (RSV), in Children with Hemodynamically Significant Congenital Heart Disease

Objectives:

The primary objective was to describe the safety and tolerability of motavizumab when given monthly as prophylaxis against serious RSV infection among children with hemodynamically significant congenital heart disease (CHD). The secondary objectives of this study were:

1. To describe the incidence of RSV hospitalization in children with hemodynamically significant CHD given motavizumab or palivizumab for prophylaxis against serious RSV disease
2. To describe the incidence of RSV outpatient medically-attended lower respiratory infection (MA-LRI) in each treatment group (for subjects randomized in Season 2 only)
3. To describe the pharmacokinetics and immunogenicity of motavizumab
4. To describe the effect of cardiopulmonary bypass on serum motavizumab concentrations

Evaluation Criteria

Safety:

Adverse events (AEs), serious adverse events (SAEs), and concomitant medications were collected from the period immediately following the first administration of study drug through Study Day 150. Blood was collected prior to the first and last doses of study drug for serum chemistries (AST, ALT, BUN, and creatinine) as part of the safety evaluation; vital signs were measured prior to and 30 minutes after each dose of study drug. Subjects were evaluated just prior to each dose of study drug, with a final post-dosing follow-up evaluation at Study Day 150.

Study Design:

Infants ≤ 24 months of age with documented, hemodynamically significant congenital heart disease were randomized in a 1:1 ratio to receive motavizumab or palivizumab at 15 mg/kg by IM injection every 30 days for a total of 5 injections. Subjects were monitored throughout the study for all hospitalizations during Seasons 1 and 2 and for outpatient medically-attended lower respiratory (MA-LR) illnesses during Season 2. Subjects hospitalized for a cardiac/respiratory illness (other than planned surgical procedures not associated with an acute illness), or whenever a cardiac/respiratory deterioration occurred during an admission, were assessed for RSV by diagnostic testing of respiratory secretions. Subjects with an outpatient MA-LR illness had nasal secretions collected that were tested for RSV. RSV testing was performed centrally using a validated real-time reverse-transcriptase polymerase chain reaction (real-time RT-PCR) RSV diagnostic test for RSV A and RSV B.

Methodology

This was a Phase 2, randomized, double-blind, palivizumab-controlled, multicenter, multinational study conducted over two RSV seasons (2005-2006 and 2007-2008) in the northern hemisphere. Each subject participated only during a single RSV season. Subjects were randomized in a 1:1 ratio to receive either 15 mg/kg motavizumab or 15 mg/kg palivizumab for five monthly IM injections during RSV season.
Approximately 1400 subjects were planned for enrollment. A total of 1236 subjects were enrolled: 621 in Season 1 (2005-2006) and 615 in Season 2 (2007-2008). Subjects were randomized to palivizumab (n=612) or motavizumab (n=624).

Patient Demographics (all three studies):

Study MI-CP110

Overall, the baseline characteristics of study participants were balanced between the two study arms. Chronic Lung Disease (CLD) of prematurity patients made up approximately 21-22% of the ITT population in both study arms. Thirty-nine percent of patients were from North America, predominantly from the United States thirty-seven percent from the European Union and the remaining twenty-four percent from what the applicant termed, the Rest of the World (ROW). The demographics of this population do differ from those of the palivizumab registrational study 018. In study 018, 50% of participants had Bronchopulmonary dysplasia (BPD) versus 22% of study 110 having a similar entity Chronic Lung Disease (of prematurity) (CLD). In study 018, 84% of participants compared to 58% in study 110 had gestational age ≤ 32 weeks. In study 018, 92% compared to 38% in study 110

were enrolled from North America. Lastly in study 018, 42% were non Caucasian compared to 21% in study 110.

Study MI-CP117:
Study 117 was conducted in full term Native American infants who were under the age of 6 months at enrollment. The study arms were well balanced according to age, gender, weight as well as the possible risk factors of smoker in household and other children under 6 years of age in the home. The tribal origins were balanced. There is no data that the tribes enrolled differed in RSV susceptibility.

Study MI-CP124:
Study 124 was conducted in infants ≤ 24 months of age with documented, hemodynamically significant congenital heart disease. The overall ITT population was balanced with regard to family history, hospitalization, gender, race, birth weight, weight at study entry, and gestational age. Patients receiving palivizumab had somewhat lower rates of previous cardiac surgery (50% vs 55%), higher rates of previous hypercyanotic episodes (46 (7.5%) vs 32 (5.1%)), severe pulmonary hypertension (52 (8.5%) vs 41 (6.6%) and uncontrolled cardiac failure (20 (3.3%) vs 8 (1.3%)). The mean age of subjects in both arms was approximately 8 months; the mean gestational age was 38.5 weeks,

Primary Efficacy Analysis

Primary Efficacy Endpoint
The primary efficacy endpoint utilized in the original palivizumab approval was the comparison of the incidence of RSV hospitalization (prophylaxis failure) between palivizumab and placebo. The primary efficacy endpoint used for the corresponding motavizumab studies was exactly the same, comparison of the incidence of laboratory confirmed RSV respiratory hospitalizations between study products. The major difference in the motavizumab studies was the use of a central laboratory using real-time RT-PCR technology to document RSV infection. In contrast, the palivizumab registrational trial Study 018 and trial 048 in hemodynamically significant congenital heart disease utilized local RSV assays performed at individual study sites using the then available antigen and culture based assays.

RSV assay methodology history
The original version of study MI-CP110 also briefly specified local testing but prior to any patients being enrolled it was amended to provide for a centrally performed RT-PCR-based, Hexaplex to document RSV infection. The Hexaplex® assay was selected because of the acknowledged greater sensitivity of RT-PCR in detecting RSV as well as sponsor developed in vitro data from 2004 indicating that motavizumab and palivizumab may cause interference with immunologically based detection methodologies such as might be used in local testing.

In September 2006 MedImmune notified the Agency that they had become aware of discrepancies between local positive RSV testing and negative central RT-PCR Hexaplex®. The sponsor tested 50 clinical specimens (10 previously scored RSV positive by the Hexaplex® assay) with a new real-time RT-PCR. The real-time RT-PCR assay detected all

10 Hexaplex® positives as well as an additional 7 RSV B infections. Of these 7 newly detected infections, 6 were from the palivizumab arm. On the basis of this experiment, the sponsor adopted the real-time RT-PCR assay according to the methodology published by Hu et al (2003) for all central RSV testing. In addition, all previously Hexaplex® tested respiratory secretions would be retested using the real-time RT-PCR. Approximately 550 specimens had been tested by the Hexaplex® prior to its replacement by the real-time RT-PCR.

Primary Efficacy Endpoint Results Study MI-CP110

In the intent-to-treat (ITT) analyses of MI-CP110 data, the odds ratio (OR) of Motavizumab relative to Palivizumab is 0.73 with a 95% Confidence Interval (CI) (0.50, 1.08). Since the upper bound 1.08 is less than the sponsor proposed non-inferiority margin 1.265, the sponsor claimed the study met the non-inferiority criterion for the primary endpoint. See Table E-1 which also considers non-RSV respiratory hospitalization.

Table E.1: MI-CP110 efficacy based on intent-to-treat population

MI-CP110	Motavizumab Size=3329	Palivizumab (size=3306)	OR of Motavizumab vs Palivizumab (95% C.I.)
# of Respiratory Hospitalization	248 (7.5%)	269 (8.1%)	0.91(0.76,1.09)
# of RSV Hospitalization	46 (1.4%)	62 (1.9%)	0.73(0.50,1.08)
# of Non RSV Respiratory Hospitalization	202 (6.1%)	207 (6.2%)	0.97(0.79,1 .18)

Reference: MedImmune's SDN 54 and reviewer's analysis
OR= odds ratio

Division Concerns regarding these results:

First, study 110 was powered with a two fold higher incidence of RSV respiratory hospitalizations anticipated. As a consequence, these results are fragile to the extent that nine additional hospitalized patients with RSV added to the motavizumab arm without any additional patients added to the palivizumab arm would result in loss of non-inferiority.

Second, again in study 110, motavizumab's efficacy relative to palivizumab in study MI-CP110 is driven by data from the Southern Hemisphere which represents about 9% of whole dataset. In data from the Southern Hemisphere the odds ratio for RSV hospitalizations with motavizumab relative to palivizumab is 0.16 with a 95% confidence interval (0.04, 0.70). For the Northern Hemisphere, the odds ratio for RSV hospitalizations with motavizumab relative to palivizumab is 0.88 with a 95% confidence interval (0.59, 1.33). The geographic heterogeneity of the treatment effect is significant with a p-value of 0.03.

Table E2 Resp hospitalization rate (Southern vs Northern Hemisphere) study MI-CP110

	RSV hospitalization rate	
Randomization date	Motavizumab	Palivizumab
2004 (11/01-12/15)+2005 (10/17-12/09) Northern Hemisphere	44/3035 (1.5%)	49/2995 (1.6%)
2005(04/01-05/31) Southern Hemisphere	2/294 (0.7%)	13/311 (4.2%)

Reference: MedImmune's SDN 54 and reviewer's analysis

In the US population, motavizumab does not meet non-inferiority criterion with an odds ratio relative to Palivizumab of 1.1, with the 95% CI of (0.58, 2.00).

Table E3: MI-CP 110 RSV Respiratory hospitalization rate: USA vs non USA

	RSV hospitalization rate	
Geographic	Motavizumab	Palivizumab
USA	22/1167 (1.9%)	20/1130 (1.8%)
Non USA	24/2162 (1.1%)	42/2176(1.9%)

Reference: MedImmune's study report Section 5.3.5.1.7.

Primary Efficacy Endpoint Results Study MI-CP117

In the ITT analyses of CP117 data, motavizumab appears to be superior to placebo with an odds ratio of Motavizumab relative to Placebo of 0.16 with a 95% CI (0.50, 1.08). See Table E.4 for details.

Table E.4: MI-CP117 efficacy based on intent-to-treat population

MI-CP117	Motavizumab (Size=938)	Placebo (Size=472)	OR of Motavizumab vs Palivizumab (95% C.I.)	
# of Respiratory Hospitalization	84 (9.0%)	64 (13.6%)	0.63 (0.44, 0 .89)	
# of RSV Hospitalization	13 (1.4%)	39 (8.3%)	0.16 (0.08, 0.30)	
# of Non RSV Respiratory Hospitalization	71 (7.6%)	25(5.3%)	1.46 (0.92, 2.34)	

Reference: MedImmune's SDN 54 and reviewer's analysis

Division Concerns regarding the results from trial CP117:

Potential limitations to study 117 include:

1. The odds ratio of motavizumab relative to placebo for Non-RSV Respiratory Hospitalization is 1.46, implying that motavizumab is numerically worse than placebo with respect to respiratory hospitalizations not confirmed to be related to RSV. The explanation for this finding is unknown but it was not observed in any other trials or other populations.

Primary Efficacy Endpoint Results Study 124

Study 124 was designed primarily to answer safety concerns regarding the use of motavizumab in patients with hemodynamically significant congenital heart disease. None-the-less, an intent to treat analysis of respiratory hospitalizations appears to indicate differences in efficacy between the two seasons of study with nearly identical results in 2005 but substantial differences favoring motavizumab in 2007 (See Table E3). As previously noted in population demographics, there was a slight imbalance of patients with higher rates of previous hypercyanotic episodes, severe pulmonary hypertension, and uncontrolled cardiac failure among palivizumab patients.

Table E.5: MI-CP124 efficacy based on intent-to-treat population

MI-CP 124	Motavizumab (Size=623)	Palivizumab (size=612)
all	12/623 (1.9%)	16/612(2.6%)
2005 season	7/319 (2.2%)	7/302 (2.3%)
2007 season	5/304 (1.6%)	9/310(2.9%)

Division Concerns regarding these results:
There is no explanation for the wide swings in apparent efficacy of both products between 2005 season and the 2007 season. The imbalance in disease severity markers among palivizumab patients compromises the ability to assess relative activities of the products.

Secondary Efficacy Analysis
In MI-CP110, the sponsor also proposed several secondary efficacy analyses. One of these secondary efficacy endpoints appears to demonstrate superiority of motavizumab over palivizumab. This endpoint is RSV-specific medically-attended lower respiratory illness (MALRI) in the MALRI subset of selected sites. In this subset analysis, the overall RSV-specific MALRI rate was 3.9% (n=46) for palivizumab recipients compared to 2.0% (n=24) for motavizumab recipients. The significance level of this analysis is 0.005. Please see Table E6.

Table E6 Rates of MALRI and RSV MALRI events Subset Population

	Motavizumab	Palivizumab	P value (Fisher's Exact test)
Total Population	1227	1183	
Total no. MALRI *Events/total population	235/1227 19.2%	251/1183 21.2%	0.223
%RSV/Total MALRI Events	24/235 10.2%	46/251 18.3%	0.014
%RSV MALRI/Total population	24/1227 2%	46/1183 3.9%	0.005

***= number of patients with at least one MALRI episode**

Division Concerns regarding these results:
Since the analysis of this endpoint was only evaluated in a subset of pre-defined study sites, it may not be representative of the entire population. In addition, it is noted that18 of the 133 substudy sites (14%) had a mixture of both subset and non-subset participants. Also, there is a substantial rate of missing data of 19% in the motavizumab groups and 18% in the palivizumab group due to missing RSV samples. Finally, the average interval between onset of symptoms and sample collection date for central RSV testing is longer for motavizumab at 3.22 days than palivizumab at 2.78 days. We expect that, the average level of RSV viral load of outpatients could be lower than that of RSV-hospitalized patients. The delay in sample collection for central laboratory analysis could further reduce the RSV viral loads of outpatients and compromise detection of RSV RNA in patient samples.

PRIMARY ENDPOINT EFFICACY ISSUES LEADING TO COMPLETE RESPONSE (CR) LETTER

Local RSV testing practice Data:
During the 2008 review of studies MI-CP110 and MI-CP117, it became clear that local RSV testing had been performed in a portion of the respiratory hospitalizations. Although many of these tests appeared to have been done on the same day as admission, in some instances they were performed 24 or more hours prior to hospital admission. The local testing data, however, were fragmentary, nearly exclusively positive results and were noted to have higher frequency in the palivizumab arm. Discussion with the sponsor determined that MedImmune held that the decision to hospitalize a participant with a respiratory illness would be made entirely on clinical assessment. In the sponsor's view local RSV testing would not be used to assist hospitalization decisions but could contribute to infection control practice after admission in accordance with local standards of care. As a consequence, local testing practice, methodology, and results were neither standardized nor systematically captured.

The Division was uncertain that local RSV testing posed no threat of systematic bias. In the Division's initial assessment, local RSV testing may have guided hospital admission decisions for patients whose clinical status was such that a decision to hospitalize the patient or to clearly discharge to outpatient management was not straightforward..

The initial attempt to characterize local RSV testing practice was the joint development of an Investigator Questionnaire by MedImmune and the Division. This questionnaire solicited site-specific practice data on the local RSV testing from all the investigators. Approximately 49% of investigative sites responded to the questionnaire. Of these 94% had local RSV testing available and 70% indicated that local tests might be used for diagnosis, admission decisions or follow-up more than 10% of the time. A small percentage of responding sites indicated that they would do local RSV tests 100% of the time for all respiratory admissions. Despite the obvious limitations of this survey it appeared to the Division that local testing may have been used in an unknown proportion of instances to influence admission decisions.

The fact that all local RSV testing data were not available to support the sponsor's contention of no impact on the primary endpoint was very concerning. In order to remedy this situation, MedImmune undertook a comprehensive chart review assessing local RSV testing practice for all patients with respiratory hospitalizations/deteriorations and medically assisted lower respiratory Infection (MALRI) patients for studies 110 and 117. Because of the extensive effort required, the chart review was not able to be completed during the 2008 review cycle.

Local RSV Assay Detection Issues:
At this point, the issue of study drug interference in local RSV testing emerged. As previously indicated the sponsor was aware that both motavizumab and palivizumab interfered with some local commercially available immunologic assays with differing of intensity. This may occur based on the fact that motavizumab and palivizumab demonstrate a high binding-affinity for an antigenically conserved domain of the RSV fusion (F) protein. Several commercially available RSV diagnostic immunoassays depend upon binding of their

own RSV F protein-specific monoclonal antibody to identify virus. The presence of motavizumab or palivizumab could compete with the assays' antibodies for binding and reduce sensitivity. The sponsor conducted in vitro experiments which indicated that both motavizumab and palivizumab interfered with detection of RSV A by Binax NOW, a popular antigen based assay. The manufacturer of this assay was aware of palivizumab's interference with their product's performance and included this information in their 2003 label. It was noted, however that interference by motavizumab occurred at a concentration five times lower than that of palivizumab. The potential for interference with RSV B with either product was not tested prior to or during the conduct of studies MI-CP110 or MI-CP117.

During the conduct of the trial, the sponsor notified investigators by letter of the local test interference issue but indicated that it was a theoretical concern and did not caution against the use of any local testing methodology.
To better assess the magnitude of potential assay interference the Division asked MedImmune to investigate the ability of motavizumab and palivizumab to interfere with RSV A and RSV B detection by local RSV assays likely to have been used in the clinical studies.

Central RSV Assay Performance:
In contrast to the in vitro interference seen with some of the local assays, the sponsor's in vitro experiments found no evidence of interference of either product with the performance of the real-time RT-PCR used in the central assay. Experiments the sponsor performed during the 2008 review did indicate that the central real-time RT-PCR had limitations however. In response to Agency requests during the 2008 review, the sponsor provided results from an experiment of a modified real-time RT-PCR assay on 13 specimens from motavizumab patients not participating in study MI-CP110 or MI-CP117 with local positive results and negative central real-time RT-PCR test results. This modified real-time RT-PCR assay found 3 additional RSV positives, all RSV B. The overall assessment, however was that the central RSV assay was not a likely source of bias since there did not appear to be difference between the assay detection abilities by product.

ANSWERS TO THE PRIMARY ENDPOINT COMPLETE RESPONSE (CR) EFFICACY ISSUES

Results of the Chart Review

Populations with Local RSV testing status known and unknown:
The sponsor reports a 95% success rate in conducting a chart review assessing local RSV testing practice for all respiratory hospitalization (Hosp) and all patients meeting the criteria for the diagnosis of medically attended lower respiratory infections MALRI. The actual corresponding numbers for these two populations are 716 respiratory hospitalizations, 646 MALRI from the MALRI substudy sites and 1454 from the MALRI non-substudy sites. Local RSV testing status is not known for 960 patients who despite having a central RSV test sample collected were subsequently determined by on-site investigators not to meet the criteria for a lower respiratory infection. Central real-time RT-PCR was not performed on these samples.

FINDINGS:

Local RSV testing associated with respiratory hospitalizations:
The results of the chart review indicated that local RSV testing was commonly performed among respiratory hospitalization patients in both studies. In study 110, overall 62% of motavizumab and 72% of palivizumab patients undergoing respiratory admission had documentation of local testing. In study 117, 66% of motavizumab and 81% of placebo respiratory admissions had evidence of local RSV testing. As will be discussed subsequently, the percentages of respiratory admissions with local testing varied considerably by geographic location.

The role this local testing played in respiratory admissions has been a source of disagreement between the sponsor and the Division. The sponsor contends that testing was only used for infection control purposes following admission. The Division contends that at least a portion of this testing preceded admission and may have been a factor in the decision to admit. The chart review attempted to clarify the local test use through comparison of test result availability and exact times admission orders were written. This hasn't settled the issue, however, since it is likely that some test results were available prior to official reporting and for approximately 40% of respiratory admissions missing data precludes determination of the sequence of local testing and admission orders.

Local RSV testing in subjects with Medically Attended Lower Respiratory Infection (MALRI):
There are two distinct MALRI populations. The first population is made up of those patients enrolled at one of the MALRI subset participating sites. If a patient from one of the subset participating sites developed clinical evidence of a lower respiratory infection as assessed by a health care provider, then a nasal specimen would be submitted for central real-time RT-PCR. Among this MALRI population the chart audit determined 66/376 (18%) motavizumab and 62/344 (18%) palivizumab had either documented or unknown local testing. The sponsor maintains the remaining patients were documented as having no local testing performed. The potential of false negative or unknown local RSV testing to bias results is low in this population when central testing results are available. The second MALRI population represents the patients developing medically attended local respiratory infection (MALRI) while enrolled at a site that had elected not to participate in the MALRI subset. In this second (non-subset) population, local RSV testing was determined to occur less frequently with, 67/725 (9%) motavizumab and 53/651 (11%) palivizumab patients having either documented or unknown local testing performed. Again, the sponsor maintains the remainder of this population was documented as having no local RSV testing performed during the respective AE/SAE.

Division Concerns regarding these results:
First, the explanation why local testing practice was numerically more frequent in MALRI subset patients compared to non-MALRI subset patients is not known. Second, no central RSV tests were performed for non-subset MALRI patients unless they were subsequently hospitalized. As a result the potential impact of local RSV testing for this small fraction of MALRI patients can not be directly assessed. An attempt was made to indirectly assess the

impact, however. The sponsor used these patients along with a few missed central testing from the MALRI subset group to perform their sensitivity analysis.

Local RSV testing issues:
The chart review indicated that a multitude of local RSV testing methodologies were used across the many countries participating in study 110. This heterogeneity of testing, the known low sensitivity of many local assays, and previous data suggesting interference prompted the Division to ask MedImmune to determine if motavizumab and palivizumab interfered with the performance of approved RSV diagnostic immunoassays used at clinical sites during studies MI-CP110 and MI-CP117.

MedImmune conducted a study to determine the effect of motavizumab and palivizumab on the sensitivities of commercially available FDA-approved RSV diagnostic assays. The immunoassays that were tested included rapid RSV-antigen detection chromatographic/enzyme immunoassays (CIA/EIA) and immunofluorescence assays (IFA). RSV detection by CIA/EIA involves the antibody-capture of RSV proteins to a solid medium and a colorimetric response. These assays typically require little or no training, few sample-processing steps, and provide rapid results—often in as few as 10 to 15 minutes. However, these assays have also been reported to have low sensitivities, often less than 60%, when compared to reverse transcriptase polymerase chain reaction (RT-PCR)–based methodologies. RSV detection by IFA relies upon the microscopic identification of RSV-infected cells by the binding of RSV-specific antibodies labeled with a chemiluminescent probe. Results from these assays can be expected within 1-2 days, have been reported to exhibit higher RSV-sensitivity than CIA/EIA, but require more technical expertise and specialized equipment. Approximately 50% of local RSV-diagnostic assays were CIA/EIA, approximately 25% IFA, and the remainder either other test types (12%) or not reported (17%).

MedImmune's assay inhibition analyses were completed using two commercially-available laboratory strains of RSV, RSV A2 and RSV B/Wash/18537/62, diluted to a titer of $1x10^4$ plaque-forming units (PFU)/mL—the limit of detection for the CIA/EIA and IFA assays in the absence of motavizumab or palivizumab. Assays were performed according to the manufacturers' instructions in the presence of 5 or 50 mcg/mL of motavizumab or palivizumab, which represented at least a 10-fold higher drug concentration than has been measured in clinical nasal wash specimens collected after intravenous administration of 15 or 30 mg/kg motavizumab (MI-CP016).

Under the laboratory test conditions, motavizumab and palivizumab interfered with RSV diagnostic assays that are designed to detect RSV F protein. Of the 10 CIA/EIA assays that were tested, 7 demonstrated interference by motavizumab and/or palivizumab. The degree of interference ranged from complete inhibition (i.e., false-negative result) to a reduction of positive-signal intensity (e.g., from "moderate" to "weak" scoring by a blinded analyst). In general, greater assay interference was observed with motavizumab than palivizumab, particularly for the detection of RSV B. Three CIA/EIA assays which utilize antibodies specific for RSV nucleocapsid protein were unaffected by either motavizumab or palivizumab. Although the presence of motavizumab or palivizumab did not alter the results

of the 7 tested IFA diagnostic kits, reductions in the numbers of positively stained cells were noted, and it is conceivable that a loss of sensitivity could occur if lower titrations of virus, such as might occur in clinical samples, were tested.

The sponsor noted that there were nearly twice as many hospitalization events in MI-CP110 with false-negative local RSV test results on samples collected from subjects in the motavizumab arm compared to those from the palivizumab arm, suggesting that motavizumab exhibited greater interference than palivizumab on local diagnostic tests. However, quantifying the impact of motavizumab and palivizumab on local testing of clinical samples is difficult to determine, and it is unclear if the differences in false-negative rates between treatment arms can be attributed to drug interference. CIA/EIA tests shown to be susceptible to motavizumab/palivizumab interference in laboratory tests produced positive-results from samples collected within both treatment arms in concordance with the central laboratory's real-time RT-PCR assay. It is possible that active drug concentrations within the respiratory tracts of prophylaxis failures were insufficient to affect local diagnostic assays. Indeed, drug-resistant viruses were identified among few isolates of prophylaxis failures, indicating that in most cases RSV replicated without the selective pressure expected at even low concentrations of the drugs.

An alternative explanation for the different immunoassay sensitivities between the motavizumab and palivizumab arms is that motavizumab was more effective than palivizumab at reducing RSV replication, thereby reducing the amount of viral antigen present in subject secretions to below the immunoassays' limits of detection. Analysis of RSV RNA levels indicated that viral loads were higher in samples positive for local immunoassays than in negative samples. However, comparable RNA loads between treatment arms and the absence of evidence for selective pressure in prophylaxis failure viruses are inconsistent with the hypothesis that motavizumab exerted a higher level of antiviral activity. Similarly, the apparent differences in immunoassay sensitivity between the treatment arms in MI-CP110 could have been due to differential activity of motavizumab and palivizumab for RSV A and RSV B. Although neither of these alternative hypotheses are unequivocally supported by the limited data, both could potentially explain the noted imbalance in false-negative rates between MI-CP110's treatment arms without local diagnostic assay interference.

There were many uncontrolled variables in the use of RSV diagnostic assays at local sites, including the use of many different types of assays with different levels of sensitivity and the potential for significant RSV antigenic and pathogenic heterogeneity among the multinational studies that spanned multiple RSV seasons. In conclusion, the data are insufficient to determine the extent to which motavizumab and palivizumab interfered with clinical RSV diagnostic immunoassays or quantitate what if any impact that interference had on biasing a physician's decision to hospitalize patients.

Sponsor Proposed Sensitivity Analysis

The sponsor proposed to address the issue of possible bias induced by the use of local RSV testing through the following two major sensitivity analyses. For the first one, through retrieval of the respective CRFs during the comprehensive chart review of study 110, the

sponsor was able to identify 45 motavizumab and 50 palivizumab MALRI patients who had either a negative or unknown status local test result and who did not have a central test result. Patients with these characteristics were selected because they resembled patients who might have been admitted except for a false negative local RSV test. Proportions of these subjects were designated as being false negative and were contributed to a primary endpoint in the sensitivity analysis.

For purposes of this analysis, the differential interference of local tests by motavizumab compared to palivizumab observed in the clinical trial was increased from 2 fold to 8 fold worse. As shown below, this analysis resulted in the addition of 2 palivizumab and 8 motavizumab primary endpoints (RSV hospitalizations). Even with these additional endpoints, the non-inferiority of the primary efficacy endpoint was maintained.

The second sensitivity analysis was conducted in a similar manner. The sponsor identified 150 motavizumab and 171 palivizumab MARI (Medically attended respiratory infections (MALRI plus MAURI)) patients who had either a negative or unknown status local test result and did not have a central test result. In this sensitivity analysis, motavizumab failed to meet the noninferiority criterion.

Table E.7: CP110 efficacy sensitivity analysis MALRI patients with neg/unk local and unknown central tests

CP110	Palivizumab (size=3306)	Motavizumab Size=3329	OR of Motavizumab vs Pali (95% C.I.)
# of RSV Hospitalization (Primary analysis)	62 (1.9%)	46 (1.4%)	0.73(0.50,1.08)
# of RSV Hospitalization (Sensitivity analysis MALRI)	62+2 (1.9%)	46+8 (1.6%)	0.84(0.59,1 .19)
# of RSV Hospitalization (Sensitivity analysis MARI)	62+11 (2.1%)	46+37 (2.5%)	1.13(0.82,1,56)

This analysis simplified sponsor reported sensitivity analyses (stratified sensitivity analysis) without distorting their results and conclusions.

Division Concerns regarding these results:
This sensitivity analysis is predicated upon local testing rates among MALRI patients of 11.7% in motavizumab and 12.6% rates in palivizumab MALRI patients (Table 5.1.2-1 in Sec 5.3.5.3.7). These local testing frequencies appear to be lower than the values reported in the investigatory survey in which local testing was thought to be used about 25% of the time to assist hospitalization decisions.

4. SUMMARY OF SAFETY DATA

General Overview of Adverse Events:
As shown below, approximately 86% of participants in both study arms experienced adverse events (AEs) during the conduct of these trials. Serious adverse events (SAEs) including hospitalizations were numerically greater in the palivizumab arm but the percentages of patients experiencing SAEs were the same across study arms. Similar patterns were seen with

those patients experiencing grade 3 and 4 adverse events. There were twice as many deaths and more withdrawals among patients in the motavizumab arm compared to the palivizumab arm.

SAFETY OVERVIEW (TABLE S1)

Overall, the safety profile of motavizumab and palivizumab is similar across the Phase 3 study CP-110 and the safety trial CP-124 (Table S1). Additionally, the overall safety profile was similar between motavizumab and placebo in study CP-117 in Native American patients. It should be emphasized that the patient populations for each of these three studies is different and this is reflected in the frequency, types and severity of adverse events. In CP-110, the patients are prematurely born and/or have chronic lung disease. Many of these patients have respiratory and neurological complications of their underlying disease process. This patient population has a higher risk for apnea, acute life threatening events and sudden death as compared to healthy infants with no underlying condition. In CP-124, the patients with hemodynamically significant congenital heart disease are at higher risk of death due to their abnormal cardiovascular and/or respiratory system and post-surgical complications of their corrective cardiac procedure. In CP-117, the Native American population has been previously noted to have a undefined increased susceptibility to RSV and other infections both bacterial and viral. The highest frequency of Grade 3 & 4 adverse events and serious adverse events was in the Phase 2 safety study CP-124 that involved RSV prophylaxis of infants with hemodynamically significant congenital heart disease.

Numerically, there were more deaths in the motivizumab treatment arm (8 deaths) than in the palivizumab arm (4 deaths) in study CP-110 for motavizumab (Table S2). This difference may be explained, in part, by two additional sudden infant death syndrome (SIDS) fatalities in the motivizumab arm. The Agency's concern about differences in SIDS and acute life threatening events (ALTE) between the motavizumab and palivizumab arms in this study was satisfactorily addressed in MedImmune's current submission, the difference observed does not appear to represent a treatment related safety signal at this point.

Hypersensitivity reactions with motavizumab are the primary safety concern for the risk/benefit assessment. Hypersensitivity reactions were observed throughout motavizumab's development and constitute the major adverse event prompting safety discontinuation in the two Phase 3 studies CP-110 and CP-117. The most common hypersensitivity reactions of concern were urticaria and allergic skin rash occurring within two days of dosing. There were also reports of angioedema in motavizumab patients which lead to discontinuation from the study. There were no reports of cardiovascular compromise or severe respiratory distress related to an allergic reaction for motavizumab in any of the submitted clinical trials. However, there were adverse event reports of allergic reactions with hoarseness, dry cough, or wheezing following study drug administration which could have represented early anaphylaxis in motavizumab patients. These reports of severe reactions coupled with the finding that the overall the frequency of urticaria and allergic rash was three fold higher among patients who received motavizumab compared to those receiving palivizumab highlights our concerns. There appeared to be a linkage between the presence of anti-drug antibodies (ADA) and hypersensitivity events among motavizumab recipients.

Those demonstrated to have motavizumab ADA were noted to have at least a 20 fold increase in frequency of hypersensitivity events compared to other motavizumab patients without evidence of ADA. No similar association was observed with palivizumab patients.

In study CP-110, as will be subsequently discussed, an increased incidence of certain types of neurological AEs (such as abnormal eye movements and muscle tone abnormalities) was observed among patients who received motavizumab compared to those who received palivizumab. These neurological AEs were analyzed by an independent consultant for MedImmune and no etiological link to motavizumab could be discerned in a population that already has an increased incidence of neurological abnormalities compared to full term healthy infants.

TABLE S1 SUMMARY OF ADVERSE EVENTS

Proportion of Patients with Any Event								
	MI-CP110		MI-CP124		MI-CP117		Pooled	
	Mota	Pali	Mota	Pali	Mota	Placebo	Mota	Pali
Event	N=3315	N=3298	N=618	N=612	N=936	N=470	N=4320	N=3993
AE	85.6%	86.0%	93.0%	92.5%	96.3%	96.8%	87.0%	86.8%
Level 3 AE	8.7%	9.40%	29.8%	33.2%	20.4%	24.3%	12.0%	12.9%
Level 4 AE	1.6%	1.80%	10.4%	11.1%	4.2%	4.5%	3.2%	3.2%
SAE	14.6%	15.30%	47.2%	49.7%	16.0%	17.7%	19.0%	20.4%
AE Resulting in Discontinuation	0.4%	0.3%	0	0.2%	0.3%	0	0.3%	0.3%

DEATHS (See Table S2 and List S3)

When all three studies are combined, there were slightly more deaths among patients receiving motavizumab compared to those receiving palivizumab (0.5% versus 0.4%). In CP-110, there were twice as many deaths in patients receiving motavizumab (8/3315) as compared to those who received palivizumab (4/3298). In CP-110 which consisted of prematurely born and/or chronic lung disease patients, SIDS was the most common cause of death and was twice as numerous among motavizumab patients at four instances as among palivizumab patients at two instances. Despite the apparent imbalance this did not reach statistical significance given the small number of events. Additionally, deaths due to airway and respiratory disease are not unexpected in this study population. In CP-124, the increased frequency of deaths (1.5-1.6%) including “sudden death”, is anticipated in a study population with underlying hemodynamically significant congenital heart disease. In CP-117, the preventable deaths (head injuries, including non-accidental trauma and co-sleeping (suffocation of infant by parent sleeping in the same bed)) can not be attributed to study drug and/or placebo; and one death in each treatment arm due to infection is within the range of expected.

TABLE S2 DEATHS

Study	Mota	Pali	Placebo
CP-110	8/3315 [0.2%]	4/3298 [0.1%]	
CP-124	9/618 [1.5%]	10/612 [1.6%]	
CP-117	3/936 [0.3%]		2/470 [0.4%]
Overall CP-110, 124, 117	20/4320 [0.5%]	14/3993 [0.4%]	

LISTING S3 CAUSES OF DEATH

- CP110 Palizumab: (total 4) 2-SIDS (2/3298) 1 Obstructive airway, 1 hemolytic uremic syndrome s/p RSV
- CP-110 Motavizumab: (total 8) 4 SIDS (4/3315) 2-pulmonary hypertension, 1-pneumonia, 1- aspiration
- CP124 Palizumab (Total 10) 7- Sudden death in cardiac pt.,1-pulm atresia, 1-pneumonia (RSV status unknown), 1-bronchiolitis (RSV status unknown)
- CP-124 Motavizumab (Total 9) 4-Sudden death in cardiac pt., 2-post-surgery cardiac death, 2-sepsis, 1-Tetrology of Fallot crisis with cyanosis

- CP117 Placebo: (Total 2) 1 co-sleeping death, 1-gastroenteritis-related
- CP117 Motavizumab: (Total 3) 1-sepsis, 2-head injuries (?non accidental death)

STUDY DISCONTINUATIONS

The overall rate of study discontinuation due to adverse events was 0.3 to 0.4% in CP-110 and CP-117 for patients receiving active product (not placebo). In CP-124, very low discontinuation rates of 0 motavizumab patients and 1 palivizumab patient (0.16%) were observed. Review of the study discontinuations for CP-110, CP-124 and CP-117 revealed that the majority of the discontinuations among motavizumab-treated patients were due to hypersensitivity reactions such as urticaria and facial angioedema. In CP-110, 9/13 (69%) of the motavizumab discontinuations were due to hypersensitivity adverse events compared to no hypersensitivity discontinuations among palivizumab-treated patients. Non-hypersensitivity reasons for discontinuations in the motavizumab arm included fever and infectious causes. Reasons for the 10 discontinuations in the palivizumab arm in the same study included neurological, respiratory/pulmonary, hematological events, and an acute life threatening event (ALTE). In CP-117, two out of the three discontinuations were due to the discovery of an underlying condition that met exclusion criteria for the study. The remaining single discontinuation in CP 117 was a true adverse event due to a hypersensitivity event in the motavizumab arm. In CP-124, there was only one adverse event (generalized macular papular rash) in the palivizumab treatment arm which resulted in discontinuation from the study.

TABLE S4 ADVERSE EVENTS LEADING TO INVESTIGATOR INITIATED DISCONTINUATION

STUDY	MOTAVIZUMAB	PALIVIZUMAB	PLACEBO
CP-110	13 (9 HS)/3315 (0.39%)	10 (0 HS)/3298 (0.30%)	
CP-124	0	1 (1 HS)/612 (0.16%)	
CP-117**	3 (1HS)**/936 (0.32%)		0
CP-110+CP-124	13 (9 HS)/ 3933 (0.33%)	11 (1 HS) /3910 (0.28%)	

HS- HYPERSENSITIVITY RELATED INCLUDING URTICARIA AND CONCERNING RASH ** In CP-117, 2 of d/c due to discovery of underlying excluding condition therefore 1/1 of AE related D/C

S5 LISTINGS OF ADVERSE EVENTS LEADING TO STUDY DISCONTINUATIONS:

CP-110

Palivizumab 10 (0 HS)

Lethargy, convulsion, pulmonary hypertension, nystagmus, bronchiolitis, bronchiolitis , hemolytic uremic syndrome (HUS) and subsequent death, cyanosis (ALTE), breathing difficulties (rhinitis), neutropenia

Motavizumab: 13 (9 HS)

Generalized urticaria + eyelid edema, facial swelling (hypersensitivity), erythema multiforme, injection site erythema + urticaria, urticaria (second episode), pyrexia (for > 2 days), bronchitis, erythema annulare, urticaria, encephalitis (late), urticaria, generalized urticaria, bacterial abscess

CP-124

Palivizumab 1 (1 HS):

Maculopapular rash, generalized

Motavizumab: 0

CP-117

Placebo 0

Motavizumab:

1 true discontinuation for AE (1 HS)

Hypersensitivity (generalized urticaria)

2 discontinuations for discovery of an underlying condition that excludes patient from study post-enrollment:

Tetralogy of Fallot, SCID **Hypersensitivity (see Tables S6-S8):**

Motavizumab, like its parent palivizumab, is a humanized monoclonal antibody retaining some of its murine derived components in the binding region of the IgG molecule. Its

enhanced binding of the RSV F protein was developed by the reintroduction of some murine moieties thereby improving its target avidity but also carrying the potential for increased hypersensitivity in the recipient. Hypersensitivity was appreciated as a potential issue in the pre-BLA meeting and MedImmune performed focused analyses of hypersensitivity adverse events and anti-drug antibodies.

Acute Hypersensitivity Skin Reactions: Acute hypersensitivity skin reactions (< 48 hours onset) were more prominent among motavizumab than palivizumab recipients. Acute hypersensitivity skin reactions could be grouped into two essentially non-overlapping categories; urticaria and rashes. In all three studies CP-110, CP-124 and CP-117, the frequency of acute urticaria was 0.4 to 0.5% in motavizumab recipients. For allergic rash, the frequency varied from 0.4% to 0.9% for motavizumab recipients (see Table S6).

In CP-110 and CP-124, the frequency of acute (<48hours onset) urticaria for palivizumab was 0 to 0.1%. In contrast, the frequency of acute urticaria for motavizumab in these studies was 0.4 to 0.5%. From CP-110 and CP-124, we can conclude there is at least a three fold increase in acute urticaria in motavizumab recipients compared to palivizumab recipients. For allergic rash, there is a two to three fold increase in frequency when comparing motavizumab to palivizumab. If acute allergic rash and urticaria are grouped together, motavizumab has a three to five fold increase in frequency of these events as compared to palivizumab. Of interest from the original palivizumab "pivotal" trial CP-018, the overall allergic reaction frequency (acute and delayed) in palivizumab recipients was 0.4% (4/1002 patients) as compared to a frequency of 0.2% (1/500 patients) in placebo recipients. Additionally, in CP-018 there was only one serious adverse event attributed to an allergic reaction at a frequency of 0.1% (1/1002 patients).

Table S6 Acute Hypersensitivity (<48 hours) in Studies CP-110, 124 and CP-117

STUDY	Motavizumab		Palivizumab		Placebo	
	Urticaria	Al. Rash	Urticaria	Al. Rash	Urticaria	Al. Rash
110	13/3315 (0.4%)	29/3315 (0.9%)	4/3298 (0.1%)	9/3298 (0.3%)		
124*	3/618 (0.5%)	2/618 (0.4%)	0	1/612 (0.2%)		
117	5/936 (0.5%)	6/936 (0.6%)			0	0

In addition to a three-fold higher incidence of acute hypersensitivity skin reactions in motavizumab recipients than in palivizumab recipients in study CP-110, the severity of the acute reactions was also higher in the motavizumab treatment group. All palivizumab acute hypersensitivity skin reactions were Grade 1 severity. In contrast, thirty-three percent of hypersensitivity skin reactions in the motavizumab arm were Grade 2 or 3 severities. Within the motavizumab arm, urticarial adverse events were more severe than allergic rash with 31% urticarial events noted to be grade 3 in severity compared to 7% allergic rashes.

Table S7 Acute (<24 hours) Hypersensitivity Skin Reactions Study CP-110

	Motavizumab N=3320		**Palivizumab N=3298**	
Total Skin Reactions	**42 (1.3%)**		**13 (0.4%)**	
	Urticarial	Allergic Rash	Urticarial	Allergic Rash
Total subjects	13 (0.4%)	29 (0.9%)	4 (0.1%)	9 (0.3%)
Severity				
Grade 1	7/13 (54%)	21/29 (72%)	4/4 (100%)	9/9 (100%)
Grade 2	2/13 (15%)	6/29 (21%)	0	0
Grade 3	4/13 (31%)	2/29 (7%)	0	0
Grade 4	0	0	0	0
CLD	5/13 (38%)	6/29 (21%)	0	2/9 (22%)
Onset in relation to dose				
Dose 1	1/13 (8%)	4/29 (14%)		1/9 (11%)
Dose 2	6/13 (46%)	8/29 (28%)	2/4 (50%)	3/9 (33%)
Dose 3	4/13 (31%)	4/29(14%)		0
Dose 4	1/13 (8%)	6/29 (21%)		3/9 (33%)
Dose 5	1/13 (8%)	7/29 (24%)	2/4 (50%)	2/9 (22%)

The term “hypersensitivity” did not always convey the patient’s complete clinical picture. In CP-110 for example, there were four adverse events in motavizumab treated patients classified as “hypersensitivity” or “drug hypersensitivity” involving facial or body edema with or without skin findings occurring within 48 hours of a motavizumab dose that appeared suggestive of angioedema. No corresponding cases were observed with palivizumab administration.

There were no recorded episodes of life threatening anaphylaxis occurring within 48 hours of study drug administration for either study drug yet there were several examples of hypersensitivity reactions (<48 hours) with clinical symptoms characteristic of early anaphylaxis occurring with motavizumab which were emergently treated and did not progress to a diagnosis of anaphylaxis. Three illustrative cases from studies CP-124, CP-117 and the Phase 1/2 study 118 are reproduced below:

CP-124:
This White female subject from Eastern Europe was 42 weeks gestation and 14.3 months of age at enrollment with an atrial septal defect and a history of bilateral otitis media, congenital pneumonia, and body mass below the 10th percentile. She received five doses of study drug, with the first dose given on 24Nov and the fifth dose given on 20Mar. On 20Mar, on the day of receipt of Dose 5 (Study Day 116), the subject was reported to have Level 3 drug hypersensitivity (judged by the site investigator as probably related to study drug) following administration of the fifth dose of study drug; age at SAE onset was 18.1 months. The subject had received study drug at 09:30 hours. Approximately 1 hour later, she experienced severe urticaria on her face, torso, and legs, with edema noted on her cheeks and hoarseness. No new medication or new food product had been introduced recently and the subject had no previous history of drug allergies or sensitivities. Vital signs remained normal. She was given hydrocortisone intravenously followed by oral Clemastine and oral calcium. By 12:00 hours, the urticaria and edema on the cheeks had disappeared. The subject was observed for two hours and was subsequently released home in good condition. The event of drug hypersensitivity resolved on 20Mar. Upon examination the following day (21Mar), the subject showed no signs of the reaction. No event of drug hypersensitivity had been reported following the previous four doses of study drug. The event of drug hypersensitivity occurred after the fifth and final dose of study drug with no further doses of study drug given. The subject was followed for safety through Study Day 150 (23Apr).

CP-117
This Native American female patient was 2.3 months of age at enrollment with a history of RAD, asthma, and an erythematous maculopapular rash. She received her fifth and final dose of study drug on 14 March. On Study Day 119, the same day following dose 5, the patient experienced hypersensitivity (Level 3, judged probably related to study drug) with symptoms of swelling of the eyes, face and fingers, erythema of the face and arms, and mild wheezing in the right upper lobe; age at AE onset was 6.2 months. She was treated with intramuscular Benadryl and solumedrol, and inhaled albuterol and steroids; the event resolved the same day. Subsequently, the patient experienced Level 1 events of URI, otitis media and gastroenteritis, and Level 3 pyrexia. All of these adverse events were judged not related to study drug, all required treatment except for the gastroenteritis, and all resolved.

CP-118
This 16.3-month-old, 34-week gestational age Hispanic female, with a history of atopic dermatitis, enrolled in the study on 31/May/05 and received her 3rd dose of MEDI-524 on 26Jul. No AEs consistent with hypersensitivity were reported after her first 2 doses of study drug. At the time of her Study Day 60 visit, the patient was in good condition with a mild cold that had onset on 18Jul for which she was not taking any medications. Fifteen minutes after receiving her 3rd dose, the patient experienced a dry cough (without stridor or difficulty breathing), periorbital erythema, and similar lesions on her back and neck (without pruritus), and mild palpebral edema; treatment with chlorprimeton 3mg IM was initiated. Approximately 15 minutes later, the patient's cough and palpebral edema and some skin lesions had decreased, while new lesions around her nose and mouth appeared. The patient was administered 10 mg oral prednisone and, one-half hour later, her facial lesions had

decreased significantly and she continued to improve. The event was considered resolved the same day, and the patient was sent home on a 5-day treatment with oral hydroxizine and prednisone. No anti-motavizumab binding activity was detected at any time point during the study. Further dosing with MEDI-524 was discontinued but safety follow-up continued as per protocol through study completion

These results would imply that motavizumab carries an increased risk of severe hypersensitivity reactions. Patients with chronic lung disease (CLD) receiving motavizumab but not those receiving palivizumab developed urticaria. The significance of this finding is not known. In both treatment groups, acute hypersensitivity skin reactions occurred most frequently after the second injection. There was a single episode of an immediate urticarial reaction noted with the first injection in a motavizumab patient.

Anti-Drug-Antibodies (ADA) and Skin/Hypersensitivity Findings (Table S8)
We examined the potential relationship of anti-drug antibodies (ADA) to motavizumab and hypersensitivity adverse events, and noted at least a 15-fold increase in the frequency of acute (<48 hours) hypersensitivity events in patients who had detectable motavizumab ADA as shown in Table S8. This association was also noted in motavizumab patients who had a specific (hypersensitivity related) skin adverse events within two days of dosing. Additionally, the presence of motavizumab ADA was associated with Grade 3 or greater adverse events, serious adverse evens, or adverse event leading to discontinuation in comparison to patients receiving motavizumab without detectable ADA. This association was not found in palivizumab patients with ADAs.

Table S8 Rate Summary of AEs of Interest by ADA in the Pooled Analysis of CP104, CP110, CP124, and MI-CP127

	ADA to Palivizumab		ADA to Motavizumab	
	Not Detected N=3778	**Detected N=46(1.2%)**	**Not Detected N=4137**	**Detected N=75 (1.8%)**
Skin Events of Interest	206 (5.5%)	2 (4.3%)	295 (7.1%)	23 (30.7%)
≥ 1 Level 3 AE or Level 4 AE or SAE	3 (0.1%)	0 (0.0%)	15 (0.4%)	8 (10.7%)
≥ 1 AE Leading to Discontinuation of Study Drug	1 (0.0%)	0 (0.0%)	4 (0.1%)	6 (8.0%)
≥ 1 AE ≤ 2 Days after Dosing	24 (0.6%)	0 (0.0%)	51 (1.2%)	14 (18.7%)
≥ 1 Non-specific AE	164 (5.5%)	2 (4.3%)	223 (5.4%)	10 (13.3%)
≥ 1 Non-specific AE ≤ 2 Days after Dosing	15 (0.4%)	0 (0.0%)	32 (0.8%)	5 (6.7%)
≥ 1 Specific AE	47 (1.2%)	0 (0.0%)	78 (1.9%)	16 (21.3%)
≥ 1 Specific AE ≤ 2 Days After Dosing	9 (0.2%)	0 (0.0%)	20 (0.5%)	10 (13.3%)

REVIEWER COMMENT (HYPERSENSITIVITY)
In these studies, hypersensitivity reactions, including urticaria and allergic skin eruptions were reported more frequently in patients receiving motavizumab than palivizumab. Additionally, we identified an association between hypersensitivity reactions and the presence of motavizumab ADA. Urticaria and allergic rash were reported three times more frequently with motavizumab (approximately 1.2%) than with palivizumab (0.4%); and urticaria reactions were more severe with motavizumab. In the "pivotal" CP-110 trial, almost half of the urticaria reactions were Grade 2 and 3 with motavizumab; while none of the urticaria reactions with palivizumab were considered greater than Grade 1. Additionally, 69% of the study discontinuations in motavizumab patients in Study CP-110 were due to hypersensitivity reactions; while none of the study discontinuations for palivizumab patients were for hypersensitivity adverse events. There were several examples of hypersensitivity reactions in motavizumab treated patients in Phase 1-3 studies which included either dry cough, hoarseness, or wheezing in addition to angioedema and/or urticaria that were possible early anaphylaxis reactions.

It is not clear at this time whether the increased level of hypersensitivity reactions, including allergic skin reactions, and angioedema along with several episodes of concomitant hoarseness, dry cough, or wheezing for motavizumab observed in clinical trials involving less than 10,000 patients signifies a potential increased risk of life-threatening anaphylaxis reactions when administered to a larger population of approximately 100,000 or more infants at risk of severe RSV disease in the U.S. Although no episodes of life-threatening anaphylaxis reactions were observed in motavizumab's clinical trials, the number of patients exposed is too small to detect an event that may occur at 1 in 100,000 patients. Currently, by evaluation of post-marketing reports, we estimate that anaphylaxis with palivizumab occurs at a frequency of 0.5 per 100,000 and would be considered "rare". If the anaphylaxis rate was three fold higher, as observed with motavizumab hypersensitivity reactions in these clinical trials, the rate would be 1.5 per 100,000.

To place the potential hypersensitivity signal for motavizumab in perspective, we compared the frequency of hypersensitivity reactions observed in these clinical trials with that reported for other therapeutic injectable monoclonals such as natalizumab (Tysabri® used to treat multiple sclerosis) and with vaccines. Natalizumab has been associated with hypersensitivity reactions, including severe systemic reactions (e.g. anaphylaxis), that occur at a frequency of less than 1%. Symptoms associated with these reactions include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. These reactions were generally associated with antibodies to natalizumab. Multiple sclerosis is a severe life threatening disease in which the risk –benefit considerations for natalizumab differ from that for a prophylactic monoclonal antibody such as palivizumab or motavizumab used to prevent RSV infections and hospitalization. Classic vaccination or active immunization involves the introduction of an antigen to elicit an immune response in a generally healthy population to prevent serious and life threatening infections. The anaphylaxis rate for vaccines is approximately 0.65 per million doses or 0.065 per 100,000, which is about eight fold less than palivizumab. However, because vaccines elicit an innate host antibody response rather than provide antibody directly, comparison of anaphylaxis rates observed with vaccine or monoclonal antibody administration are not directly comparable. The hypersensitivity findings clearly

suggest that motavizumab has more hypersensitivity reactions than palivizumab with at least 3-fold higher rate of acute urticaria and allergic rash and a at lest six-fold higher rate of angioedema in the patient population of prematurely born infants and infants with chronic lung disease who would be the primary recipients of RSV prophylaxis, if motavizumab were marketed. The hypersensitivity findings from natalizumab suggest the possibility that the association between hypersensitivity reactions and ADA for motavizumab may predict more severe possibly life-threatening reactions when a larger population of infants and toddlers are exposed to multiple doses of motavizumab for RSV prophylaxis.

Neurological Adverse Events

In our 2008 review of study 110, we noted an increase in the number of neurological SAEs with motavizumab compared to palivizumab. On closer examination, two categories of neurologic SAEs appeared to account for the increases. The first was muscle tone abnormalities excluding hypotonia. Among these there were 4 motavizumab patients (0.1%) versus no palivizumab patients. The second SAE category was lethargy which involved 3 motavizumab patients (0.1%) and no palivizumab patients. Increases in muscle tone AEs other than hypotonia were also noted in study 110 as well as in earlier phase 2 studies CP-104 and CP-127, motavizumab (1.9%) versus palivizumab (1.3%). Other neurologic AEs that appeared in study 110 to have increased frequency with motavizumab use included abnormal eye movements and inflammatory CNS inflammatory adverse events (encephalitis, meningitis, and brain abscess) events. At the Agency's request, MedImmune analyzed the neurological events from CP-110, CP-117 and CP-124 and also had an independent external reviewer perform both a blinded and unblinded review of neurological adverse events. The independent consultant confirmed the differences between motavizumab and palivizumab observed in CP-110; however noted the trends were not observed in CP-124 or CP-117 where placebo was the comparator. The independent consultant could not identify any etiology to explain the increased frequency of these neurologic events in motavizumab patients.

RISK-BENEFIT

Although the sponsor contends that motavizumab has comparable activity to palivizumab, the studies were potentially biased with regard to the primary efficacy endpoint determination. We clearly have a safety signal suggesting that motavizumab has more significant hypersensitivity reactions than palivizumab. The safety data from other injectable humanized monoclonal antibody products like natalizumab suggest there may be a link between anti-drug antibodies and severe hypersensitivity reactions. An association between anti-drug antibodies and hypersensitivity reactions does appear to exist for motavizumab. This association does not exist for palivizumab. We do not know if this association observed with motavizumab will also predict an increased risk of life threatening hypersensitivity reactions should it be licensed. We are confident, however, that the studies to date clearly establish motavizumab as being more immunogenic than palivizumab and as having a marked increase in the frequency of moderate to severe hypersensitivity reactions including study discontinuations based on investigator concern. To this point, palivizumab has demonstrated efficacy with a relatively low number of post-marketing reports of hypersensitivity (approximately 60 AEs) including eight reports of anaphylaxis in the context of more than 1.2 million infant and toddlers exposed.