U.S. Food and Drug Administration

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Motavizumab

RSV Monoclonal Antibody

Antiviral Drugs
Advisory Committee Meeting

June 2, 2010

MedImmune

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Proposed Indication

- **Motavizumab is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease.**
- **These populations are:**
  - **Infants with a history of premature birth (≤ 35 weeks gestational age)**
  - **Children with chronic lung disease (CLD) of prematurity**
  - **Children with hemodynamically significant congenital heart disease (CHD)**

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Background

- Synagis® (palivizumab)
  - FDA approved in June 1998
  - Remains the only approved agent for RSV prophylaxis
    - Binds to a conserved neutralizing epitope on RSV F protein and prevents essential steps of the infection process
- Motavizumab
  - Developed as an effective agent for RSV prophylaxis
    - Developed by *in vitro* affinity maturation of palivizumab
    - Same binding site and mechanism as palivizumab

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Several Lines of Preclinical Evidence Demonstrated Greater Motavizumab Activity Compared to Palivizumab

- Higher binding affinity for RSV F protein
- Greater *in vitro* neutralizing activity against clinical RSV isolates
- Significantly reduced RSV viral load in the upper and lower respiratory tracts in the cotton rat model of RSV infection
- Significantly reduced RSV-induced long-term airway hyper-responsiveness in the mouse model

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Regulatory Interactions

- End of Phase II meeting: May, 2005
- Pre-BLA meeting: January, 2007
- BLA submitted: January, 2008
- Complete Response Letter:
  - Received: November, 2008
  - Response: December, 2009

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Overview of the Complete Response Letter

- Efficacy
  - Performance of the central lab real time RT-PCR
  - Effect of motavizumab and palivizumab on locally performed RSV tests
  - Consistency of efficacy results within subgroups
  - RSV subtype exposure during the studies
- Safety
  - External expert review of deaths and neurologic AEs
- Timing of ADA assay and sensitivity of assay in presence of motavizumab
- Submit final report for MI-CP124 (Congenital Heart Disease Study)

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Sponsor Presentation

- Introduction – Ross Lobell
- RSV Overview – Octavio Ramilo, MD
- Efficacy – Pam Griffin, MD
- Safety – Genny Losonsky, MD
- Benefit-Risk Assessment – Mark Boguniewicz, MD
  Octavio Ramilo, MD
- Post-Approval Activities – Greg Geba, MD, MPH

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Invited Subject Matter Experts

- **Mark Boguniewicz, MD**
  Professor, Pediatric Allergy-Immunology,
  National Jewish Health and University of Colorado School of Medicine
- **Andrew Colin, MD**
  Professor, Pediatric Pulmonology, University of Miami
- **Tim Feltes, MD**
  Chair, Pediatric Cardiology, Nationwide Children's Hospital, Columbus, OH
- **Octavio Ramilo, MD**
  Chair, Pediatric Infectious Diseases
  Nationwide Children's Hospital, Columbus, OH
- **Sarbjit Saini, MD**
  Professor, Allergy and Immunology, The Johns Hopkins University
- **Janet Wittes, PhD**
  President, Statistics Collaborative, Inc.

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Sponsor Responders

- **Don Cilla,** *Product Team Leadership*
- **Iksung Cho,** *Biostatistics*
- **Gregory Geba,** *Clinical Development*
- **Pam Griffin,** *Clinical Development*
- **Brian Harris,** *Biostatistics*
- **Ross Lobell,** *Regulatory Affairs*
- **Genny Losonsky,** *Clinical Development*
- **Gabriel Robbie,** *Translational Sciences*
- **Sarah Stanton,** *Patient Safety*
- **JoAnn Suzich,** *Research*

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RSV Overview

Octavio Ramilo, MD

Professor of Pediatrics
Chair of Pediatric Infectious Diseases

Nationwide Children's Hospital, Columbus, OH

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Worldwide Burden of RSV Disease

- Major viral respiratory pathogen in children
  - ~50% of infants are infected in 1st year of life
  - ~90% infected by 2 years of age
- Within the 1st year of life, ~ 25% of RSV infected children have an LRI (lower respiratory infection)
- Compared to influenza, RSV associated with higher rates of ED visits, hospitalizations and caregiver resource use
  - Twice as many ED visits (23.6% vs 11.2%)
  - Six times more hospitalizations (8.5 vs 1.4 per 1000 term children)
  - Caregivers lose 3 times more workdays

Fisher RG, et al. *Pediatrics*. 1997;99:E7; Glezen et al *NEJM* 1973; Broughton S, et al. *Thorax,* 2005;60:1039-44; Brandt CD, et al. *Am J Epidem*. 1973; 98:355–64; Henderson FW, et al. *J Pediatr*. 1979;95:183–90; La Via WV, et al. *J Pediatr*. 1992;121:503–10; Bourgeois FT, et al. Pediatrics 2009;124:e1072-1080

Burden of RSV LRI: Hospitalization

- RSV is leading cause of hospitalization in infants <1yr
  - ~125,000 hospitalizations in US annually (CDC)

	General Population Term Children	High-risk Children
Rates of hospitalization	1%-2.9%	5%-10%
Hospitalization Mean LOS (days)	3.4	5-7
Require ICU care	3%-9%	10%-50%
ICU Mean LOS (days)	3.4	4.5-7.2
Require mechanical ventilation	1.5%	17%-40%

LOS: length of stay

Boyce TG, et al. *J Pediatr*. 2000;137:865–70; Joffe S, et al. *Pediatrics*. 1999;104:419–427; Shay DK, et al. *JAMA*. 1999; 282:1440–6; Griffin MR, et al. *Arch Int Med*. 2002;162:1229–36. Bockova J, et al. *Pediatrics*. 2002;110:e20; Horn SD, et al. *J Pediatr*. 2003:143:S133-S141; Moler FW, et al. *Crit Care Med*. 1992;20:1216–22; Forbes ML, et al. *J Med Econ*. 2010;13:136–41.

Acute Consequences of RSV LRI

- Most LRIs due to RSV are outpatient events (MA-LRI)
- RSV adversely affects pulmonary function
  - RSV LRI causes severe small airway inflammation
  - Increases airway resistance, air trapping, atelectasis, and affects ventilation/perfusion ratio
- RSV MA-LRI in preterm infants
  - Increases hospital re-admissions
  - Causes recurrent wheezing throughout childhood
  - Decreases lung function for at least 1 year after RSV LRI
- RSV MA-LRI in Hemodynamically significant CHD
  - Acute and persistent cardiovascular effects
  - Complicates management of patients requiring surgical correction or palliation

MA-LRI=medically attended lower respiratory infection

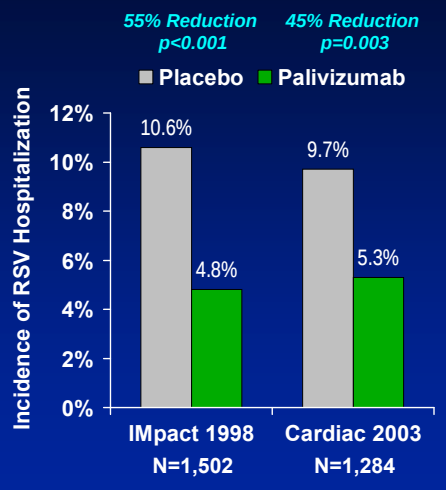
Bourgeois FT, et al. Pediatrics 2009;124:e1072-1080; Broughton S, et al. *Arch Dis Child.* 2006;91:26–30; Broughton S, et al. *Thorax.* 2005;60:1039–44; Broughton S, et al. *Pediatr Infect Dis J.* 2007;26:1019–24; Altman CA, et al. *Pediatr Cardiol.* 2000; 21:433–438

Current Standard of Diagnosis and Care

- No RSV vaccine available
- No effective anti-RSV treatment available for an already established infection
- Hospitalization decisions are based on clinical assessment
  - Local testing not recommended for admission decisions (2006 AAP bronchiolitis guidelines)

Challenges to Current Standard of Care

- Palivizumab is the standard of care for prevention in high-risk infants
  - Typical course is 5 doses
  - No data on RSV outpatient MA-LRI
- Decreased RSV hospitalization or outpatient MA-LRI would offer meaningful clinical benefit



The IMpact-RSV Study Group. *Pediatrics*. 1998;102:531–537; Feltes TF, et al. *J Pediatr*. 2003;14: 532–540

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Efficacy

Pam Griffin, MD

Senior Director, Clinical Development, Infectious Diseases

MedImmune

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Efficacy of Motavizumab

- **Registrational and Supportive Studies (MI-CP110, MI-CP124, MI-CP117)**
  - Study Objectives and Design
  - RSV Efficacy Data
  - RSV Hospitalization Considerations
  - Summary of RSV Efficacy Endpoints
- **Efficacy Conclusion**

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Registrational and Supportive Studies

Study	Population	Sample Size	Primary Objectives
Registrational			
MI-CP110	Premature infants w/wo chronic lung disease (CLD)	6635	• Safety • Efficacy: RSV hospitalization
MI-CP124	Children with hemodynamically significant CHD	1236	• Safety
Supportive			
MI-CP117	Native American term infants	1410	• Safety • Efficacy: RSV hospitalization (long-term wheezing as secondary objective)

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Secondary Objectives for Registrational and Supportive Studies

	MI-CP110 (Preterm) N=6,635	MI-CP124 (CHD) N=1,236	MI-CP117 (Native American) N=1,410
RSV-Specific			
Incidence of RSV Hospitalization		Yes	
Incidence of RSV Outpatient MA-LRI	Yes [a]	Yes [b]	Yes
Non RSV-Specific (All Cause)			
Incidence of MA-LRI	Yes		
Incidence of MA-Otitis Media	Yes		Yes
Frequency of MA-Otitis Media	Yes		Yes
Antibiotics for MA-LRI	Yes		
Antibiotics for MA-Otitis Media	Yes		

a: Collected in a pre-specified subset of 2410 patients at 133 sites
b: Second season only

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Study Design: MI-CP110 (Premature Infants) and MI-CP124 (CHD)

- Multinational
- Active control: palivizumab
  - 1:1 randomization
  - 15 mg/kg monthly x 5 doses
- RSV endpoint identification
  - Hospitalization: admission or deterioration for respiratory illness
  - Outpatient MA-LRI: children with signs of lower respiratory illness seen by health care professional
  - Investigators directed to obtain respiratory secretions within 2 days of admission/deterioration or outpatient illness
- RSV endpoints determined by real-time RT-PCR
  - Performed by central lab (Beckman Coulter, formerly Cogenics)
- Safety and efficacy follow-up for 150 days

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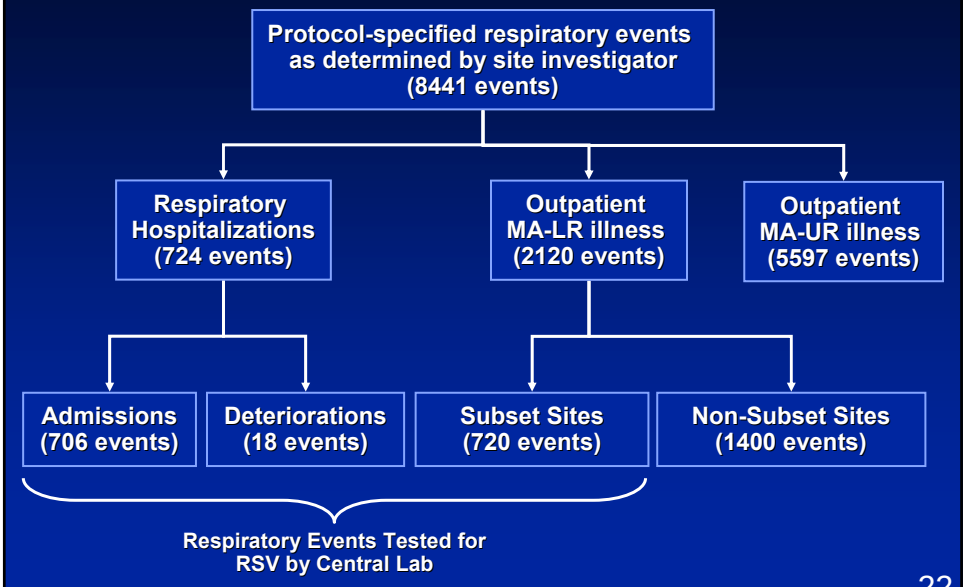
Collection of Respiratory Events in MI-CP110



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Baseline Characteristics and Study Compliance in the Registrational and Supportive Studies

- Baseline characteristics were balanced between treatment groups in all 3 studies
- Patients were randomized by site and stratified by:
  - CLD of prematurity in MI-CP110
    - ~20% in each treatment group
  - Cyanotic heart lesion in MI-CP124
    - ~50% in each treatment group
- Study compliance was high and similar
  - MI-CP110:
    - Completed study: palivizumab 98.1%, motavizumab 98.2%
    - Received all 5 scheduled doses of study drug: palivizumab 96.7%, motavizumab 96.5%

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Efficacy of Motavizumab

- Registrational and Supportive Studies (MI-CP110, MI-CP124, MI-CP117)
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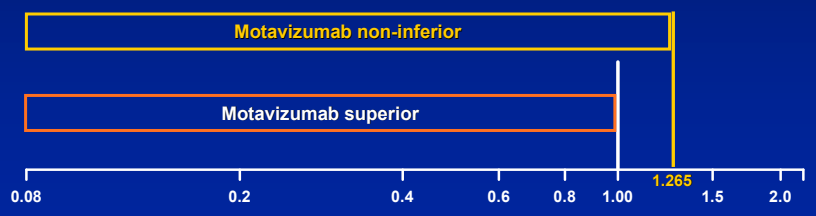
MI-CP110: Primary Efficacy Analysis Non-inferiority Margin

- Used data from prior placebo-controlled palivizumab efficacy studies in preterm and CHD populations
- Calculated to preserve 50% of benefit of palivizumab over placebo using 95-95 CI method as requested by FDA
- Non-inferiority margin: Upper bound of the 95% CI for relative risk of RSV hospitalization < 1.265



Relative Risk of RSV Hospitalization with Motavizumab vs Palivizumab

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MI-CP124: Primary Efficacy Analysis Used a Pooled Analysis Approach

- MI-CP124 was not powered to demonstrate efficacy as a stand-alone study
- Pooling data from MI-CP110 & MI-CP124 was appropriate as the studies have similar study designs, endpoints, and sample collection
- Prior to pooling the data, interaction tests demonstrated no evidence of a difference in treatment effect across study populations
- Pre-specified pooled analysis was performed using the same non-inferiority margin of 1.265

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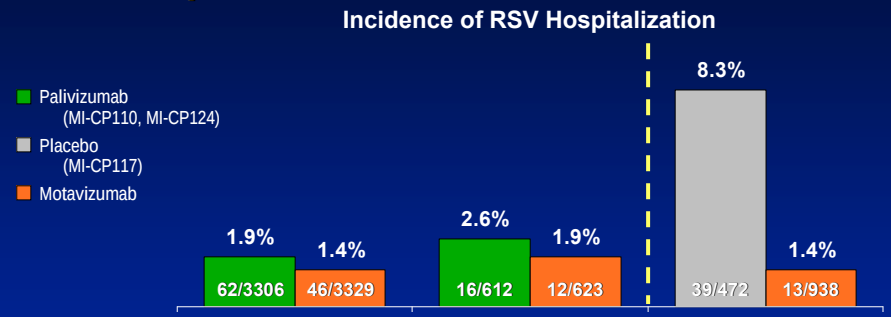
Motavizumab is Non-Inferior to Palivizumab and Superior to Placebo in Reducing RSV Hospitalizations



	MI-CP110 (Preterm)	MI-CP124 (CHD)	MI-CP117 (Native American)
Relative Risk	0.74	0.75	0.17
95% CI	(0.50, 1.08)	(0.34, 1.59)	(0.09, 0.31)
Efficacy demonstrated by motavizumab	Non-inferior to palivizumab (p<0.01)	Supportive (p=NS)	Superior to placebo (p<0.001)

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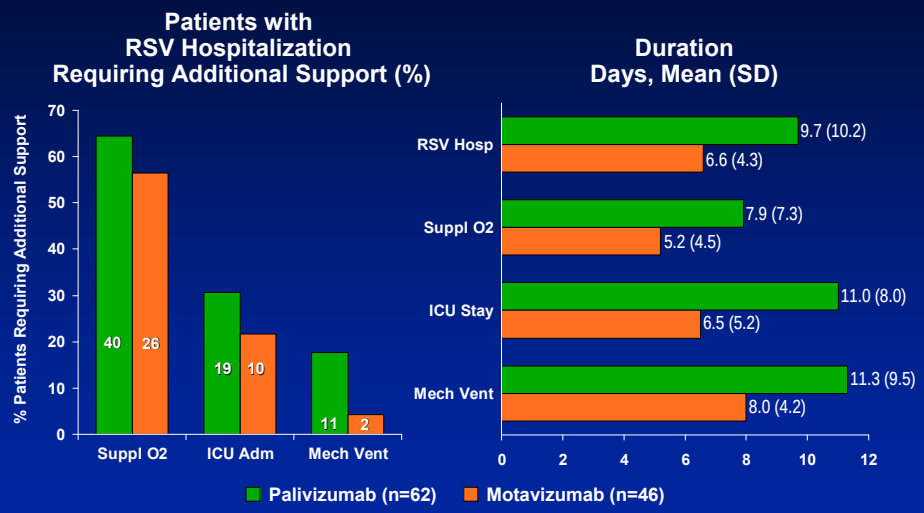
MI-CP110 (Premature Infants): Severity of Illness in Patients with RSV Hospitalization



post hoc analysis

RSV Hosp=RSV hospitalization; Suppl O2=Supplemental O_2; ICU Adm=ICU admission; Mech Vent=mechanical ventilation

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MI-CP110: Baseline Characteristics for Subset and Non-Subset Populations

	Subset Population		Non-Subset Population	
	Pali N=1,183	Mota N=1,227	Pali N=2,123	Mota N=2,102
Male, n (%)	636 (53.8%)	655 (53.4%)	1175 (55.3%)	1161 (55.2%)
White, n (%)	897 (75.8%)	940 (76.6%)	1704 (80.3%)	1672 (79.6%)
Age (mean ± SD, m)	4.2 (4.3)	4.1 (4.1)	3.9 (3.4)	3.9 (3.5)
Wt (mean ± SD, kg)	4.6 (2.2)	4.5 (2.1)	4.4 (1.9)	4.4 (1.9)
GA (mean ± SD, wks)	31.3 (3.0)	31.4 (3.0)	31.0 (3.1)	30.9 (3.1)
≤ 32 weeks GA, n (%)	671 (56.7%)	699 (57.0%)	1253 (59.0%)	1259 (59.9%)
CLD [a], n (%)	263 (22.2%)	259 (21.1%)	460 (21.7%)	463 (22.0%)

a: Stratification variable

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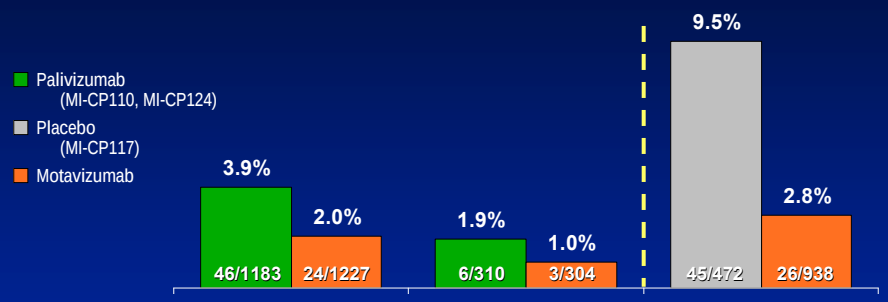
RSV Outpatient MA-LRI in Registrational and Supportive Studies

Incidence of RSV Outpatient MA-LRI



	MI-CP110 (Preterm)	MI-CP124 (CHD)	MI-CP117 (Native American)
Relative Risk	0.50	0.49	0.29
95% CI	(0.30,0.82)	(0.10,1.99)	(0.18,0.47)
Efficacy demonstrated by motavizumab	Unadjusted p=0.005	p=NS	Superior to placebo p<0.001

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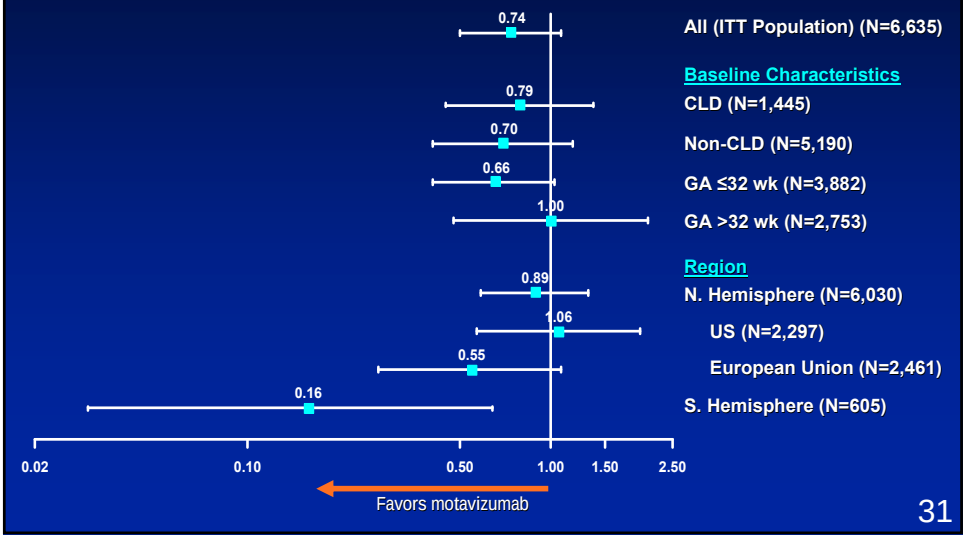
MI-CP110 (Premature Infants): Subgroup Analyses for RSV Hospitalizations

Relative Risk: Motavizumab Compared to Palivizumab



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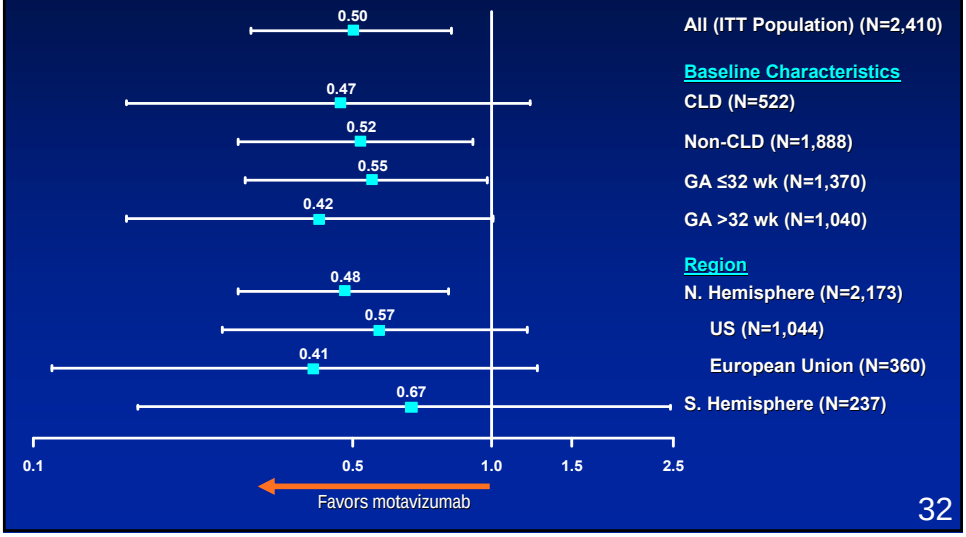
MI-CP110 (Premature Infants): Subgroup Analyses for RSV Outpatient MA-LRI (Subset Population)

Relative Risk: Motavizumab Compared to Palivizumab



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Non RSV-Specific (All Cause) Secondary Endpoints Were Not Significantly Different

		MI-CP110 (Preterm)			MI-CP117 (Native American)		
		Pali N=3,329 %	Mota N=3,306 %	Unadjusted p-value	Placebo N=472 %	Mota N=938 %	Unadjusted p-value
Incidence of MA-LRI		21.1	19.5	0.110			
Incidence of MA-Otitis Media		13.9	14.5	0.476	39.2	38.0	0.685
Frequency of Otitis Media events	1	10.0	10.8	0.500	26.5	25.8	0.553
	2	3.0	2.7		7.8	8.2	
	≥3	1.0	1.0		4.9	3.9	
Prescribed antibiotics for outpatient MA-LRI, mean (SE)		0.32 (0.02)	0.30 (0.02)	0.493			
Prescribed antibiotics for MA-Otitis Media, mean (SE)		1.08 (0.03)	1.10 (0.03)	0.652			

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Efficacy of Motavizumab

- Registrational and Supportive Studies (MI-CP110, MI-CP124, MI-CP117)
  - Study Objectives and Design
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- Efficacy Conclusion

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Local RSV Tests and Medically Attended Respiratory Illnesses

- Physicians obtained local RSV tests as desired
  - Not protocol directed
- Local RSV testing data obtained after study completion to answer FDA questions regarding potential effect on hospital admission
- Effect of anti-RSV monoclonal antibodies on local RSV tests
  - Palivizumab and motavizumab can decrease detection of RSV in local RSV test BinaxNOW® RSV
    - Notified investigators of possible false negative result with local tests (BinaxNOW® RSV)
- Collected data for >12,000 medically attended respiratory events in the 3 studies
  - Data available for ≥ 95% of medically attended respiratory events

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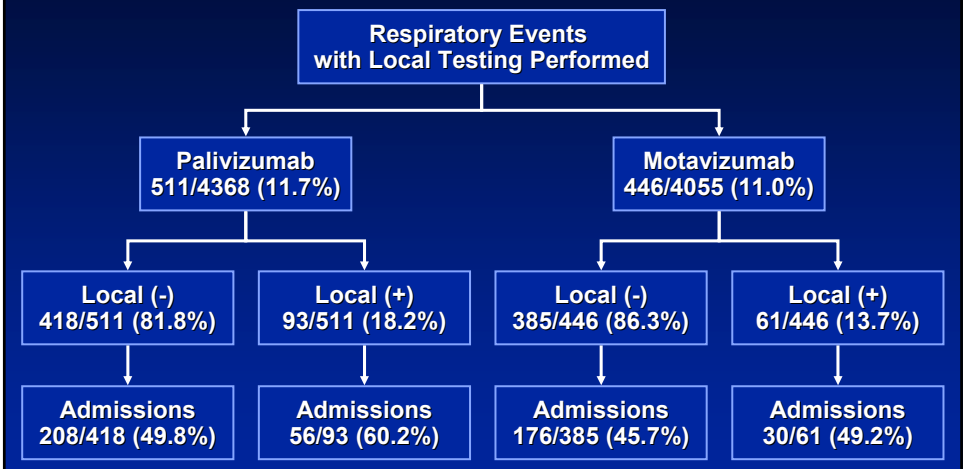
MI-CP110: Evaluation of the Effect of False Negative Local RSV Tests on Hospital Admissions



- RSV hospitalizations with false (-) local result:
  - Palivizumab 8/53 (15.1%)
  - Motavizumab 13/32 (40.6%)

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Sensitivity Analyses for the Effect of False Negative Local RSV Tests on Hospital Admissions Are Consistent With Non-Inferiority Result

- Multiple sensitivity analyses performed:
  - Events imputed as RSV hospitalizations
    - Outpatient MA-LR illness (lower respiratory illness)
    - Outpatient MA-LR illness + MA-UR illness (lower + upper)
      - Imputation with MA-UR illness is an extreme analysis
  - 4 imputation methods
    - Known false negatives and imputation of unknowns using point estimate, 95% CI, and 100% of missing events
- Results:
  - Analyses of MA-UR illness + MA-LR illness had an upper limit of 95% CI <1.265 except for 1 analysis based on the point estimate method
  - All analyses of MA-LR illness had an upper limit of 95% CI <1.265

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Efficacy of Motavizumab

- Registrational and Supportive Studies (MI-CP110, MI-CP124, MI-CP117)
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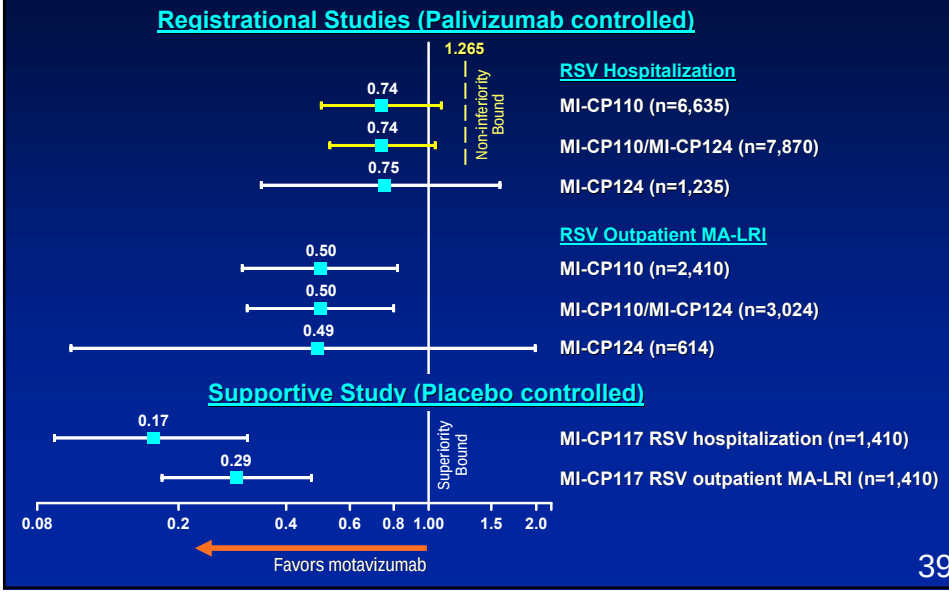
Overall Summary of Efficacy

Relative Risk: Motavizumab Compared to Palivizumab/Placebo



Efficacy Conclusion

- Motavizumab is effective in decreasing serious RSV disease in high-risk children
  - Non-inferior to palivizumab for prevention of RSV hospitalization
  - Supportive efficacy data in prevention of RSV outpatient MA-LRI
  - Supportive efficacy data in children with CHD
  - Supportive efficacy data in Native American infants

Safety

Genevieve Losonsky, MD

Vice President, Clinical Development, Infectious Diseases

MedImmune

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Safety Overview

- Exposure
- Safety Profile
  - Overall Adverse Events (AEs)
  - Skin Reactions
    - ADA
- Safety Conclusions

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Motavizumab Exposure
Pediatric Safety Database

Study Population: Study Number	Number of Patients
Registrational and Supportive Studies	
Preterm infants with/without CLD: MI-CP110	3,315
Children with hemodynamically significant CHD: MI-CP124	618
Native American term infants: MI-CP117	936
Phase 1/2 Additional Studies	
Preterm infants: MI-CP104	217
Mixed dosing: MI-CP127	259
Second season dosing: MI-CP118	66
RSV-infected term infants: MI-CP106	15
Total Patients	5,360[a]

a: Excludes 66 subjects in MI-CP118 who were counted in MI-CP104.

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Safety Overview

- Exposure
- Safety Profile
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    - ADA
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Incidence of AEs, Level 3 and 4 AEs, and SAEs in Registrational and Supportive Studies

Total number of patients (%) reporting:	MI-CP110 (Preterm) Pali N=3,298 n (%)	MI-CP110 (Preterm) Mota N=3,315 n (%)	MI-CP124 (CHD) Pali N=612 n (%)	MI-CP124 (CHD) Mota N=618 n (%)	MI-CP117 (Native American) Placebo N=470 n (%)	MI-CP117 (Native American) Mota N=936 n (%)
≥ 1 AE	2837 (86.0)	2839 (85.6)	566 (92.5)	575 (93.0)	455 (96.8)	901 (96.3)
≥ 1 Level 3 AE	311 (9.4)	289 (8.7)	203 (33.2)	184 (29.8)	114 (24.3)	191 (20.4)
≥ 1 Level 4 AE	61 (1.8)	54 (1.6)	68 (11.1)	64 (10.4)	21 (4.5)	39 (4.2)
≥ 1 SAE	506 (15.3)	485 (14.6)	304 (49.7)	292 (47.2)	83 (17.7)	150 (16.0)

Mortality Rates within Registrational and Supportive Studies

Total number of patients (%) reporting:	MI-CP110 (Preterm) Pali N=3,298 n (%)	MI-CP110 (Preterm) Mota N=3,315 n (%)	MI-CP124 (CHD) Pali N=612 n (%)	MI-CP124 (CHD) Mota N=618 n (%)	MI-CP117 (Native American) Placebo N=470 n (%)	MI-CP117 (Native American) Mota N=936 n (%)
All deaths	4 (0.1)	8 (0.2)	10 (1.6)	9 (1.5)	2 (0.4)	3 (0.3)
RSV related deaths	0	0	0	0	0	0
SIDS/sudden death	2 (0.06)	4 (0.1)	4 (0.7) [a]	4 (0.6) [a]	0	0

a: As determined by the medical monitor prior to unblinding; SIDS/sudden deaths were all sudden deaths

Patients with Dosing Discontinuation in Registrational and Supportive Studies

	MI-CP110		MI-CP124		MI-CP117	
Preferred Term	Pali N=3,298	Mota N=3,315	Pali N=612	Mota N=618	Placebo N=470	Mota N=936
Patients with dosing discont.	10 (0.3)	13 (0.4)	1 (0.2)	0	0 (0.0)	3 (0.3)
Skin/Subcutaneous [a]	0	9 (0.3) [a]	1 (0.2) [b]	0	0 (0.0)	1 (0.1) [c]
Bacterial abscess CNS	0	1 (0.0)				
Bronchitis	0	1 (0.0)				
Encephalitis	0	1 (0.0)				
Pyrexia	0	1 (0.0)				
Bronchiolitis, RSV Bronchiolitis, Rhinitis	3 (0.1)	0				
Convulsion	1 (0.0)	0				
Cyanosis	1 (0.0)	0				
Haemolytic uremic syndrome	1 (0.0)	0				
Lethargy	1 (0.0)	0				
Neutropenia	1 (0.0)	0				
Nystagmus	1 (0.0)	0				
Pulm hypertension crisis	1 (0.0)	0				
Combined immunodeficiency					0	1 (0.1)
Diarrhoea					0	1 (0.1)
Fallot's tetralogy					0	1 (0.1)

a: MI-CP110: 6 patients with urticarial AEs, 1 patient with hypersensitivity, 1 patient with erythema annulare, 1 patient with erythema multiforme
b: MI-CP124: 1 patient with maculopapular rash
c: MI-CP117: 1 patient with hypersensitivity and diarrhea

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Safety Overview

- Exposure
- Safety Profile
  - Overall Adverse Events (AEs)
  - Skin Reactions
    - ADA
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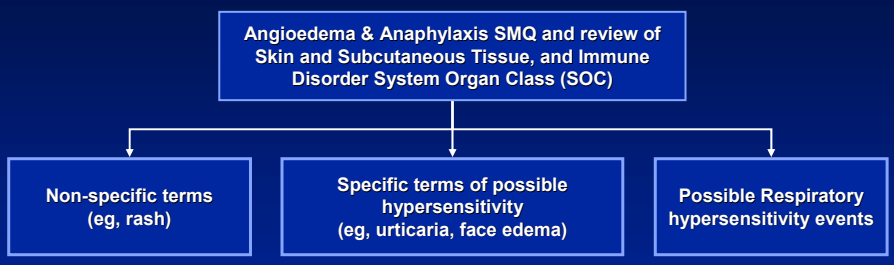
Analysis Schema for Increased AEs Reported in Skin and Subcutaneous Tissue System Organ Class (SOC) in Motavizumab Recipients



- AEs were assessed by onset ≤ 2days and >2 days from study dosing
- Consistency of the results of the comprehensive approach was assessed using individual SMQ analyses for Angioedema, Anaphylaxis, and Severe Cutaneous Reactions

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Incidence of Skin Events of Interest in Registrational and Supportive Studies

	MI-CP110 (Preterm)		MI-CP124 (CHD)		MI-CP117 (Native American)	
	Pali N=3,298 n (%)	Mota N=3,315 n (%)	Pali N=612 n (%)	Mota N=618 n (%)	Placebo N=470 n (%)	Mota N=936 n (%)
Patients reporting ≥ 1 skin event of interest	169 (5.1)	239 (7.2) *	44 (7.2)	63 (10.2)	58 (12.3)	138 (14.7)
L3, L4 or SAEs [a]	2 (0.1)	14 (0.4) *	2 (0.3)	8 (1.3)	0	6 (0.6)
Dosing discontinued [b]	0	9 (0.3)	1 (0.2)	0	0	1 (0.1)
Non-specific	135 (4.1)	177 (5.3) *	35 (5.7)	44 (7.1)	49 (10.4)	110 (11.8)
Specific	38 (1.2)	69 (2.1) *	10 (1.6)	20 (3.2)	10 (2.1)	35 (3.7)
Specific >2 days	30 (0.9)	47 (1.4)	9 (1.5)	14 (2.3)	10 (2.1)	28 (3.0)

* $p<0.05$
a: there were no Level 4 AEs reported in the motavizumab group
b: only occurred for skin events ≤2 days of dosing

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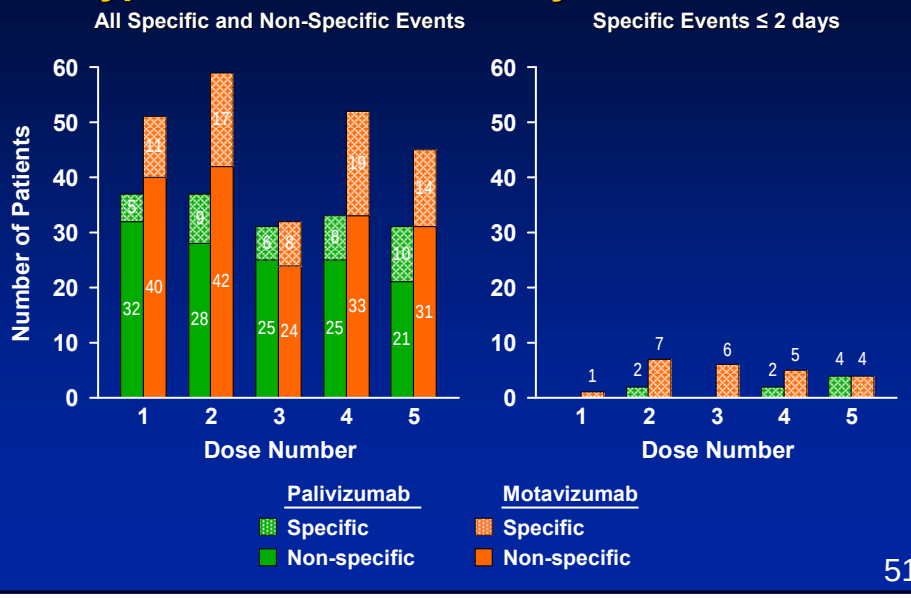
MI-CP110: Rate of Skin Events Regardless of Type are Not Increased by Dose Number



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Characteristics of Skin AEs of Interest within 2 Days of Dosing

Patients reporting ≥ 1 Skin AE of Interest	MI-CP110 (Preterm) Pali N=3,298 n (%)	MI-CP110 (Preterm) Mota N=3,315 n (%)	MI-CP124 (CHD) Pali N=612 n (%)	MI-CP124 (CHD) Mota N=618 n (%)	MI-CP117 (Native American) Placebo N=470 n (%)	MI-CP117 (Native American) Mota N=936 n (%)
Non-specific event ≤ 2 days	9 (0.3)	26 (0.8)	6 (1.0)	8 (1.3)	1 (0.2)	6 (0.6)
L3 or SAEs	0	0	1 [a]	0	0	0
Recurrences/Redosing	0/8	2/22 (9.1) [b]	0/3	1/6 (16.7) [b]	0/1	0/6
Specific event ≤ 2 days	8 (0.2)	23 (0.7) *	1 (0.2)	6 (1.0)	0	7 (0.7)
L3 or SAEs [c]	0	9 (0.3)*	0	4 (0.6)	0	5 (0.5)
Recurrences/Redosing	0/4	2/11 (18.8)	0/1	0/2	0/0	0/1

* Palivizumab vs. motavizumab $p<0.05$
a: Resulted in dosing discontinuation
b: Initial and recurrent events were mild in severity; patients received all 5 doses
c: There were no Level 4 AEs reported

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Serious/Severe Specific Skin Events on Day of Dosing in Motavizumab Patients

Study	Preferred Term	Suspect Dose (time from last dose)	Additional Findings	Treatment	Resolution Onset from AE Onset
MI-CP110	Urticaria (SAE L3)	4 (22min)	Facial edema	P	4 hr
	Urticaria (L3)	5 (1hr)	no	S	30 min [a]
	Hypersensitivity (SAE L2)	4 (3.5hr)	Facial edema alone	Oral Ca gluconate	16 hr [a]
	Drug hypersensitivity (L3)	5 (45min)	Face, hand edema, papular lesions on trunk	S, A	1 day [a]
MI-CP124	Urticaria (L3)	5 (2.25hr)	Eye edema	A	2hr
	Drug hypersensitivity (SAE L3)	5 (1.25hr)	Gen urticaria, cheek edema, hoarseness	IV hydrocortisone, A, oral Ca	1.25h [a]
	Urticaria (SAE L3)	5 (15min)	Eyelid edema	P, A	3.5 hr
MI-CP117	Hypersensitivity (SAE L1)	5 (2-3hr)	Red face, ear edema	none	1 day [a]
	Dermatitis allergic (SAE L2)	5 (2.5hr)	Gen red rash	A	8 hr [a]
	Urticaria (SAE L3)	5 (30min)	no	A	54 min
	Hypersensitivity (SAE L3)	4 (25min)	Gen urticaria, ear edema	A	1 day [a]
	Hypersensitivity (SAE L3)	5 (35-60min)	Red face, arm; eyes, face, finger edema, wheezing RUL [b]	A (IM), S, bronchodilators	90 min

A=antihistamines; P=prednisone; S=solumedrol; RUL=right upper lobe;
a: Time to complete resolution; b: baseline asthmatic on chronic therapy; 1 week history of wheezing before dose; post dosing was febrile, O_2 saturations 98%, treated for respiratory illness post dosing

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MI-CP118: Hypersensitivity Event in Second Season Dosing with Motavizumab

Preferred Term	Dose (AE onset time from dose)	Findings	Treatment	Resolution Onset from AE Onset
Hypersensitivity (L4)	3 (15min)	18 month old with dry cough, nonpruritic lesions on back and neck, mild eyelid edema and redness [c]	chlortrimeton [a, b] (intramuscular)	60 min

a: started 30 minutes post AE onset
b: sent home on prednisone and antihistamine
c: mild cold noted prior to dosing; no anti-motavizumab antibody detected 90-120 days post final dose

Vital Signs	Pre	Post (20 minutes post dose)
Blood Pressure	121/72	75/50
Heart Rate	131	101
Respiratory Rate	32	41

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Safety Overview

- Exposure
- Safety Profile
  - Overall Adverse Events (AEs)
  - Skin Reactions
    - ADA
- Safety Conclusions

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Low Frequency of Anti-Drug Antibodies (ADA) in Registrational and Supportive Studies

- < 2% of patients developed ADA following monthly prophylaxis

Study	Patients with ADA to Palivizumab	Patients with ADA to Motavizumab
MI-CP110 (Preterm)	37/3222 (1.1%)	58/3231 (1.8%)
MI-CP124 (CHD)	9/602 (1.5%)	9/605 (1.5%)
MI-CP117 (Native American)	NA	3/724 (0.4%) [a]

a: 1 (0.14%) patient had IgE ADA detected

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Skin Events in Patients with ADA in MI-CP110

Patients Reporting AE Outcome	ADA to Motavizumab MI-CP110 (Preterm) No ADA N=3,173	ADA N=58
Skin events of interest	217 (6.8%)	17 (29.3%) *
≥ 1 Specific skin events ≤ 2 days of dosing	15 (0.5%)	8 (13.8%) *
Level 3 or SAE at any time	8 (0.3%)	6 (10.3%) *
Recurrences with redosing of any skin event	21/171	5 /14
Recurrences/redosing of Level 3 or serious events ≤ 2 days	0/0	1 /2 [a]

* Motavizumab patients with vs without ADA, p<0.001
a: Recurrent event was of lower severity than initial event
Note: No skin events in patients with ADA in MI-CP117

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Safety Overview

- Exposure
- Safety Profile
  - Overall Adverse Events (AEs)
  - Skin Reactions
    - ADA
- Safety Conclusions

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Safety Conclusions

- Safety profiles of motavizumab and palivizumab are similar
  - Similar rates of reported AEs, Level 3, 4 AEs, and SAEs
  - The incidence of dosing discontinuation was low (<0.5%) and similar
    - The majority of dosing discontinuations in motavizumab, MI-CP110, were due to skin events
  - Overall, mortality was low and within expected rates for these populations
- Skin and soft tissue AEs consistent with acute hypersensitivity is the main adverse reaction
  - Rate was low (<1%) but higher in patients receiving motavizumab
  - All were easily manageable; no event consistent with anaphylaxis

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Benefit-Risk Assessment

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Risks: Safety Profile

- Motavizumab and palivizumab have similar overall safety profiles
- There is one identified potential risk for motavizumab compared to palivizumab
  - Increased but low rates of skin reactions with some features suggestive of immediate type hypersensitivity reactions
  - These were:
    - Predominantly of mild severity, easily managed, transient and non-recurrent on redosing
    - Recurrences (~10%) were no more severe than the initial events

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Benefits of Motavizumab

- The totality of the evidence demonstrates that motavizumab is effective in decreasing serious RSV disease in high-risk children
  - The reduction in RSV hospitalization demonstrates that motavizumab is non-inferior to palivizumab and superior to placebo
  - The reduction in RSV outpatient MA-LRI relative to palivizumab and placebo offers additional benefit

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Post-Approval Activities

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Recommendations to Healthcare Providers for Management of Skin Reactions

The proposed package insert advises:

- **Discontinuation of therapy for skin reactions which are:**
  - **Serious, requiring immediate medical attention, or life-threatening, or**
  - **Other reactions at the discretion of the clinician, which are temporally associated and possibly related to motavizumab**
- **For those which are not temporally associated, but possibly related, the benefits and risks should be weighed**

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Pharmacovigilance

- Targeted Monitoring for AESIs
- Risk Management Strategy
  - Educating prescribers
  - Enhanced pharmacovigilance activities
  - Post-approval clinical studies
    - Surveillance and clinical characterization of skin adverse reactions
    - Detection of rare events with retrospective cohort study

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Risk Management Strategy

- Educate prescribers
  - Labeling – specific text for safety monitoring and management
  - Medical education campaign employing team of clinical experts
- Enhanced pharmacovigilance plans
  - Expedite all serious Adverse Events of Special Interest (AESI) as 15-Day reports
  - Employ questionnaires for data collection for AESIs
  - Assess the outcomes of SAEs involving severe hypersensitivity or serious or life-threatening skin reactions
    - Determine whether drug was discontinued (as recommended in PI)
    - Determine whether additional safety information can be obtained from these cases
  - Establish an external expert panel to adjudicate skin SAEs
  - Reassess enhanced pharmacovigilance plan after 3 years

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Activities to Manage Risk: Post-Approval Clinical Studies

- **Prospective surveillance study**

  Objectives:
  1. To characterize skin and hypersensitivity events associated with motavizumab and assess their rates and severity
  2. Monitor for the emergence of possible motavizumab-resistant RSV

- **Retrospective cohort study**

  Objectives:
  1. To assess and monitor the incidence rate, relative risk and predictors of potential and unanticipated rare adverse events in a real world setting (powered for rate 1/10,000)
  2. To assess the potential risk of re-dosing motavizumab and/or sequential dosing with palivizumab in the same patient within the same season or between seasons

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Overall Conclusions

- **Motavizumab has an acceptable and manageable safety profile, and is effective for the immunoprophylaxis of serious RSV disease in high-risk children**
  - **Premature infants**
  - **Infants with chronic lung disease**
  - **Infants with congenital heart disease**
- **Overall, the efficacy showing reduction in outpatient and inpatient serious RSV disease, suggests that motavizumab is the drug of choice for immunoprophylaxis to prevent serious RSV illness in these high-risk children**
- **Post-marketing pharmacovigilance and post-approval clinical studies will permit timely and systematic collection and assessment of safety data arising in the marketplace**

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