U.S. Food and Drug Administration

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# Motavizumab

## BLA 125283/0

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Antiviral Drugs Advisory Committee Meeting

June 2, 2010

# Presentation Outline

- Efficacy Discussion
  - Overview of studies CP-110, CP-117, and CP-124
  - Determination of Non-Inferiority
  - Endpoint analysis of studies
- Safety Issues
  - Overall AE profile including deaths and study discontinuations
  - Analysis of acute hypersensitivity events including cases suggestive of anaphylaxis

# Studies to Support BLA

- Phase 1 and 2 Studies:
  - CP-101, 104, 106, 118, and 127
- Phase 3 Studies:
  - CP-110 and CP-117
- Additional Phase 2 Study to expand indication
  - CP-124 (data not submitted in original application)

# CP-110: Study Design

- Phase 3 randomized double-blind, multicenter study of RSV prophylaxis of serious RSV disease in high-risk children
  - Premature infants (gestational age< 35 weeks) less than 6 months of age
  - Chronic lung disease (CLD) less than 24 months of age

# CP-110: Endpoints

- Primary endpoint:
  - RSV hospitalization: RSV positivity determined by a central real-time RT-PCR assay
- Secondary endpoints:
  - Medically attended lower respiratory tract infections (MALRI) caused by RSV
  - All cause MALRI
  - Frequency and incidence of otitis media (OM)
  - Antibiotic use for OM and MALRI

# CP-117: Study Design

- Prevention of RSV disease among Navajo and White Mountain Apache infants
- Phase 3, randomized (2:1), double-blind, placebo-controlled trial designed to compare motavizumab to placebo
- Primary endpoint: RSV hospitalization
- Secondary endpoints: MALRI and OM

# CP-124: Study Design

- RSV prophylaxis in children with hemodynamically significant congenital heart disease comparing motavizumab to palivizumab
  - Safety trial not powered for efficacy:
    - Incidence of RSV hospitalization
    - Incidence of RSV outpatient medically-attended lower respiratory infection (MALRI) in season 2

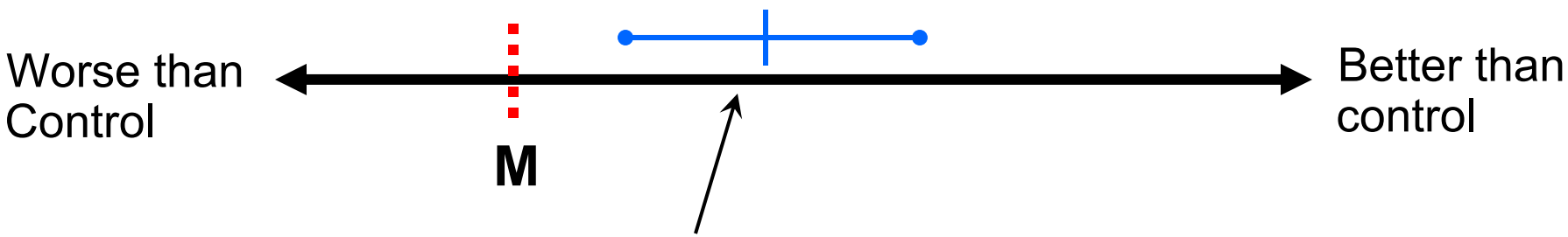
# Efficacy Results

## Efficacy Presentation Outline

- CP-110: Motavizumab vs. Palivizumab
  - Non-inferiority Margin Determination
  - Primary Endpoint
  - Primary Endpoint: Limitations of Data and Sensitivity Analyses
  - Selected Secondary Endpoint: Outpatient subset
- CP-117: Motavizumab vs. Placebo
  - Primary Endpoint
- CP-124: Motavizumab vs. Palivizumab
  - RSV Respiratory Hospitalizations

# Non-Inferiority Margin (M) Definition

"M" is the degree of inferiority of the Test Drug to an Active Control that we wish to exclude statistically in a trial.




**Confidence Interval Around the Difference or Ratio of the Treatment Effects Should not Exceed "M"**

# Determining a Margin "M"

**M1 (Ensure that new drug is better than placebo)**

- Based on historical data of the effect of Control Drug compared to placebo
- Should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.[1]

**M2 (Ensure that not too much efficacy is lost)**

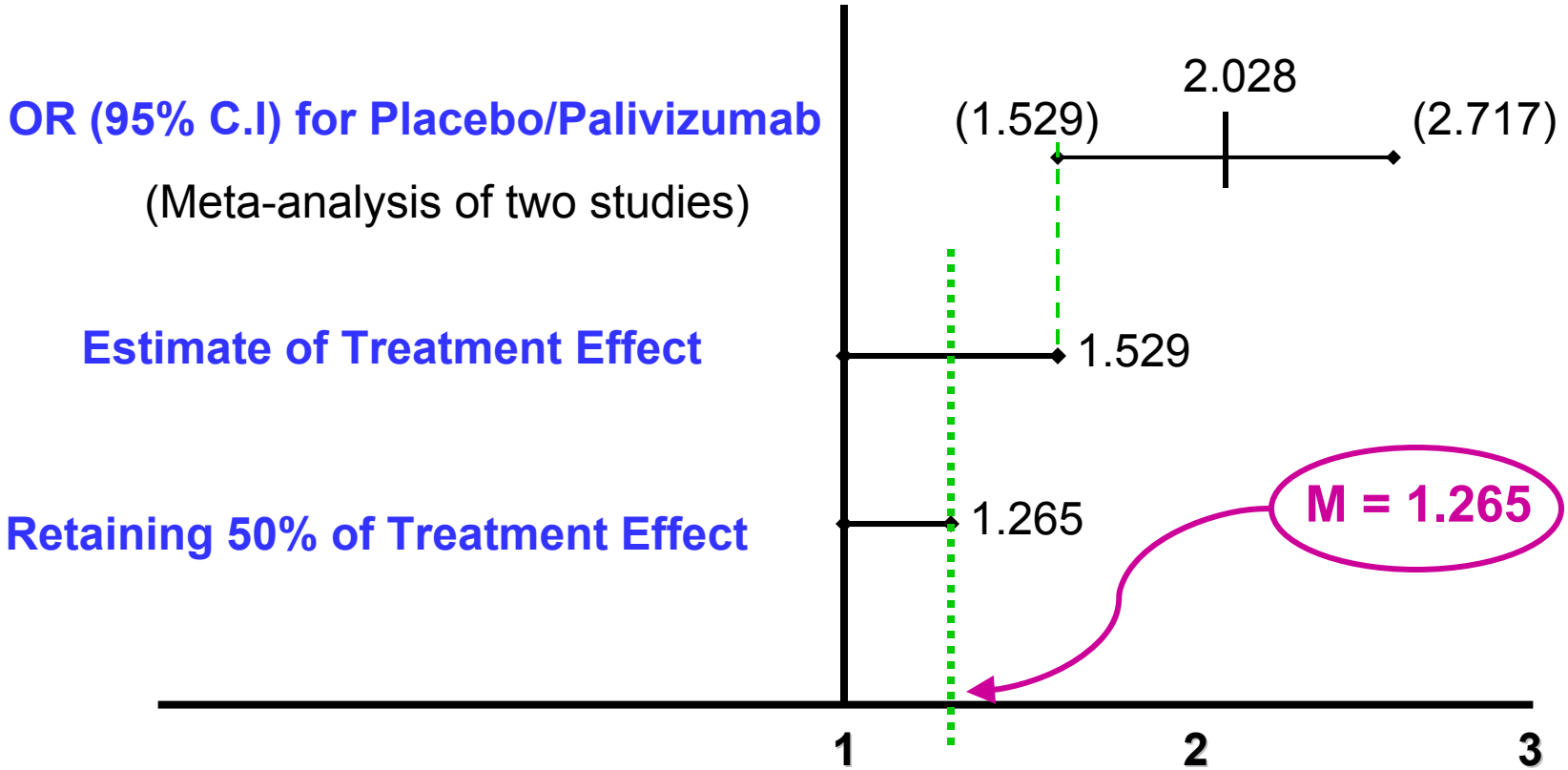
- How much efficacy are we willing to lose? Use "clinical judgment"[1]

**M: the margin used in a trial**

- Could be the entire effect of the control drug (M1)
- Or could be smaller (M2) if there is need to preserve more than just any of the control drug effect.

[1] **International Conference on Harmonisation, E10 Choice of Control Group and Related Issues in Clinical Trials**

# Calculation of "M" for Study CP-110
## For OR of Motavizumab vs. Palivizumab




**OR: Placebo/Control for RSV Hospitalization**

# CP-110 Efficacy Results

## Primary Endpoint

**ITT population**

| | **Motavizumab N = 3329** | **Palivizumab N = 3306** | **Motavizumab vs Palivizumab OR (95% C.I.)** |
|---|---|---|---|
| | | | |
| **RSV Respiratory Hospitalizations** | **46 (1.4%)** | **62 (1.9%)** | **0.73 (0.50,1.08)** |
| Total Respiratory Hospitalizations | 248 (7.5%) | 269 (8.1%) | 0.91(0.76,1.09) |
| Non-RSV Respiratory Hospitalizations | 202 (6.1%) | 207 (6.2%) | 0.97(0.79,1 .18) |

**OR = odds ratio**

# CP-110: Results of Primary Endpoint by Region

**Number (%) of RSV Respiratory Hospitalizations**

| | **Motavizumab** | **Palivizumab** |
|---|---|---|
| **Northern Hemisphere** | 44/3035 (1.5%) | 49/2995 (1.6%) |
| **Southern Hemisphere** | 2/294 (0.7%) | 13/311 (4.2%) |
| | | |
| **U.S. sites** | 22/1167 (1.9%) | 20/1130 (1.8%) |
| **Non U.S. sites** | 24/2162 (1.1%) | 42/2176 (1.9%) |

# Identified Issue in First Review Cycle

**Did local RSV testing bias RSV hospitalization decisions?**

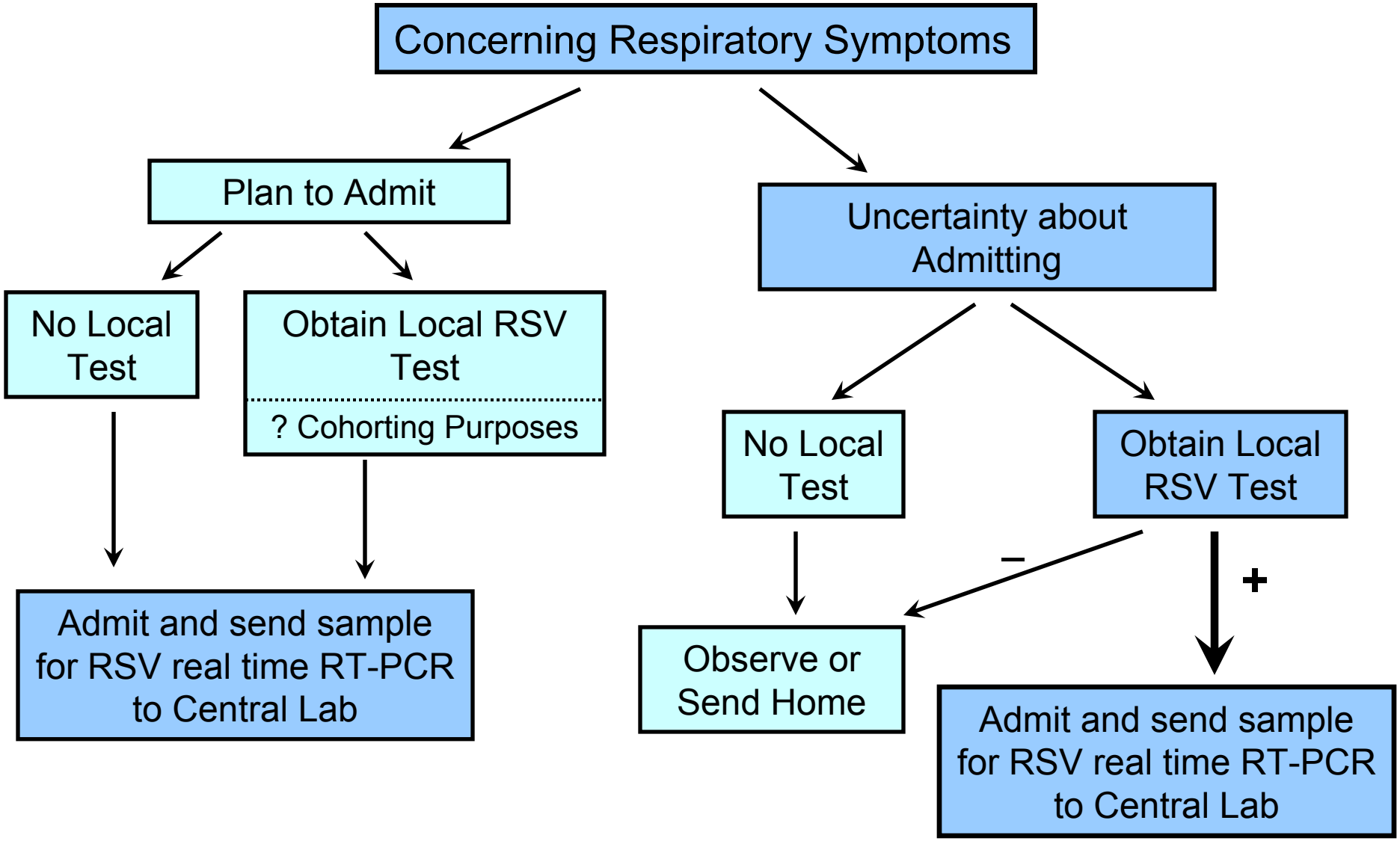
# Local RSV Testing

- Motavizumab and palivizumab compete for F protein binding sites of some local RSV assays
  - may interfere with local assay results
  - *in vitro* studies suggest motavizumab may interfere more than palivizumab

- Central testing by real-time RT-PCR in hospitalized patients in CP-110 indicates:
  - false negative local test rate twice as high in motavizumab patients compared to palivizumab

- In clinical situations where local RSV tests were used in hospitalization decisions, disparate assay performance could lead to bias

# How might local testing influence admission decisions



# Local RSV Testing

- Use of available assays permitted, but not part of study protocols
- Local testing practices not systematically documented
- Local testing was conducted in CP-110, CP-124,CP-117
  - 65-70% of hospitalized patients in CP-110 had local testing done in close proximity to admission
  - 11% of all patients with any respiratory event in CP-110 had local RSV testing
- In CP-110, approximately 50% of admitting physicians knew the results of local RSV testing prior to admission
  - possible impact on hospitalization decision for some patients

# Applicant's Response to FDA's Complete Response Letter

- Review of Case Report Forms (CRFs) and "source documents" of patients in CP-110 and CP-117 to document local testing practices:
  - All respiratory hospitalizations
  - All outpatient MALRI
    - RSV samples collected, not collected, or collected, but not run
  - Most outpatient upper respiratory illness
  - Ran previously banked not processed samples for central analysis
- Sensitivity analyses to gauge the potential bias of local testing practice on primary endpoint

# CP-110: Applicant's Sensitivity Analyses

## Two Examples from Multiple Sensitivity Analyses with FDA Confirmation

- Evaluated effects of possible bias in hospital admissions due to:
  - false-negative local RSV tests
  - tests that might have been false negative
- Analyses impute:
  - additional RSV hospitalizations based on <u>all known</u> false negative local test results; and
  - <u>a proportion</u> of potentially false-negative tests
- Analyses attempt to correct for patients who *might* have been hospitalized, but were not, because a local test was falsely negative and influenced a clinical decision not to hospitalize

# Sensitivity Analysis Example #1

## Lower Respiratory Illness

- Added all Outpatients with a Medically Attended Lower Respiratory Illness known to have a False-Negative local test
- Also Added Outpatients with Medically Attended Lower Respiratory Illness who "could have had" a false negative test based on:
  - negative or unknown local test AND no central test result
  - the proportion added was based on a probability estimation using a model of subjects with known local and central test results.

| | Motavizumab | Palivizumab |
|---|---|---|
| **"Potential" False Negatives** | 45 | 50 |
| **Estimated Additional Patients "True RSV+"** | 8 | 2 |
| **Known False Negative Local Test** | 5 | 5 |
| **Total Added to RSV Hospitalizations** | 13 | 7 |

**Non-inferiority was maintained: OR = 0.85 (0.60 to 1.20)**

# Sensitivity Analysis Example #2 Any Respiratory Illness

- Added all outpatients with any Medically Attended Respiratory Illness known to have a false negative local test
- Added outpatients with any Medically Attended Respiratory Illness who "could have had" a false negative test based on:
  - negative or unknown local test AND no central test result
  - the proportion added was based on a probability estimation using a model of subjects with known local and central test results.

| | Motavizumab | Palivizumab |
|---|---|---|
| **"Potential" False Negatives** | 211 | 228 |
| **Estimated Additional Patients "True RSV+"** | 37 | 11 |
| **Known False Negative Local Test** | 13 | 15 |
| **Total Added to RSV Hospitalizations** | 50 | 26 |

**Non-inferiority was NOT maintained: OR = 1.09 (0.81 to 1.46)**

# CP-110: Secondary Endpoint in Outpatient Study Subset

## Medically Attended Lower Respiratory Infections (MALRI)

| | **Motavizumab** | **Palivizumab** | **p-value** Fisher's Exact |
|---|---|---|---|
| RSV + MALRI | 24/1227 (2%) | 46/1183 (3.9%) | 0.005 |
| ANY MALRI | 235/1227 (19.2%) | 251/1183 (21.2%) | 0.223 |

# Limitations of Secondary Endpoint Outpatient MALRI Data

- Endpoint was only evaluated in a subset of study sites
- Substantial rate of missing data: motavizumab 19% and palivizumab 18% due to missing RSV samples
  - Missing data might result in reduction of motavizumab's estimate of benefit over palivizumab for preventing RSV MALRI

# CP-117: Motavizumab vs Placebo in Native American Children

**ITT population**

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

OR = odds ratio

# CP-124: Study in Congenital Heart Disease (CHD)

**ITT population**

| | Motavizumab N = 623 | Palivizumab N = 612 | Motavizumab vs Palivizumab OR (95% C.I.) |
|---|---|---|---|
| RSV Hospitalization | 12 (1.9%) | 16 (2.6%) | 0.73 (0.34,1.56) |

**OR = odds ratio**

# Efficacy Summary (1)

- Motavizumab met the non-inferiority criteria for the primary analysis in CP-110
- Limitations include:
  - Local test results might have influenced respiratory hospital admissions
  - Given the low event rate, the results are sensitive to misclassification of a few events
  - Applicant's sensitivity analyses may be insufficient to rule out an important impact of local testing on the primary endpoint because of uncertainty in capturing all local test results

# Efficacy Summary (2)

- CP-110: Secondary Endpoint in Study Subset
  - Fewer RSV MALRI events in subjects who received motavizumab compared to palivizumab
- CP-124: Although underpowered for efficacy, primary endpoint results were numerically consistent with those observed in CP-110
- CP-117: In Native American Children, subjects receiving motavizumab had statistically fewer RSV hospitalizations than subjects receiving placebo

# SAFETY

# Safety

- The Applicant responded to our concerns about:
  - SIDS/Apparent Life Threatening Events (ALTE)
  - Neurological AEs
  - Neutropenia
- Hypersensitivity identified in more patients who received motavizumab than palivizumab
- Cases suggestive of anaphylaxis also identified in patients receiving motavizumab

# Adverse Events in CP-110 and CP-124

| Event | CP - 110 | | CP - 124 | |
|---|---|---|---|---|
| | Motavizumab | Palivizumab | Motavizumab | Palivizumab |
| | N=3315 | N=3298 | N=618 | N=612 |
| AE | 85.6% | 86.0% | 93.0% | 92.5% |
| Grade 3/4 AE | 9.8% | 10.7% | 34.5% | 38.1% |
| SAE | 14.6% | 15.30% | 47.2% | 49.7% |
| AE Resulting in Discontinuation | 0.4% | 0.3% | 0 | 0.2% |

# Deaths

| Study | Motavizumab | Palivizumab | 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*** | 20/4869 [0.4%] | 14/3910 [0.4%] | 2/470 [0.4%] |

***CP-110, CP-124, and CP-117**

# Causes of Death CP-110

- **Motavizumab (Total 8):**
  - 4 SIDS
  - 2 pulmonary hypertension
  - 1 pneumonia
  - 1 aspiration
- **Palivizumab (Total 4):**
  - 2 SIDS
  - 1 airway obstruction
  - 1 hemolytic uremic syndrome s/p RSV

# Causes of Death CP-124

- Motavizumab (Total 9):
  - 4 sudden deaths
  - 2 post-surgery cardiac deaths
  - 2 sepsis
  - 1 Tetralogy of Fallot crisis with cyanosis
- Palivizumab (Total 10):
  - 4 sudden deaths
  - 2 cardiac arrests
  - 1 cardio-respiratory arrest
  - 1 pulmonary atresia
  - 1 pneumonia (RSV status unknown)
  - 1 bronchiolitis (RSV status unknown)

Note: Palivizumab arm had a higher proportion of patients with cyanotic heart disease and uncontrolled heart failure as compared to motavizumab patients at enrollment

# Causes of Death CP-117

- **Motavizumab (Total 3):**
  - 1 sepsis
  - 2 head injuries (accidental)
- **Placebo (Total 2):**
  - 1 co-sleeping death
  - 1 gastroenteritis-related

# AEs Leading to Discontinuations

| STUDY | MOTAVIZUMAB | PALIVIZUMAB | PLACEBO |
|---|---|---|---|
| CP-110 | 13/3315 (0.39%) | 10/3298 (0.30%) | |
| CP-124 | 0/618 | 1 /612 (0.16%) | |
| CP-110 & CP-124 | 13/3933 (0.33%) | 11/3910 (0.28%) | |
| CP-117 | 3/936 (0.32%) | | 0/470 |

# Investigator Initiated Discontinuations for CP-110 and CP-124

| Category | Motavizumab | Palivizumab |
|---|---|---|
| Hypersensitivity | 9 | 1 |
| Neurological | 1 | 3 |
| ALTE | 0 | 1 |
| Pulmonary | 1 | 4 |
| Other* | 2 | 2 |
| Total | 13 | 11 |

* Motavizumab: pyrexia, bacterial abscess; Palivizumab: HUS, neutropenia

# Acute Hypersensitivity Reactions Onset within 48 hours

| STUDY | Motavizumab | | Palivizumab | | Placebo | |
|---|---|---|---|---|---|---|
| | Urticarial | Allergic Rash | Urticarial | Allergic Rash | Urticarial | Allergic Rash |
| 110 | 12/3315 (0.4%) | 26/3315 (0.8%) | 3/3298 (0.1%) | 10/3298 (0.3%) | | |
| 124 | 7/618 (1.1%) | 6/618 (1.0%) | 2/612 (0.3%) | 3/612 (0.5%) | | |
| 117 | 4/936 (0.4%) | 6/936 (0.6%) | | | 0 | 0 |

Urticarial includes urticaria, edema, and localized erythema
Allergic Rash includes acute rash, allergic dermatitis, erythema multiforme, erythema annulare, macular papular rash

# Differences in Hypersensitivity Severity in CP-110

**Acute (<48 hours) Hypersensitivity Skin Reactions**

| | **Motavizumab N=3320** | | **Palivizumab N=3298** | |
|---|---|---|---|---|
| Total Skin Reactions | **38 (1.1%)** | | **13 (0.4%)** | |
| | Urticarial | Allergic Rash | Urticarial | Allergic Rash |
| Total subjects | 12 (0.4%) | 26 (0.8%) | 3 (0.1%) | 10 (0.3%) |
| Severity | | | | |
| Grade 1 | 4/12 (33%) | 21/26 (81%) | 3/3 (100%) | 10/10 (100%) |
| Grade 2 | 3/12 (25%) | 4/26 (15%) | 0 | 0 |
| Grade 3 | 5/12 (42%) | 1/26 (4%) | 0 | 0 |
| Grade 4 | 0 | 0 | 0 | 0 |

# CP-110 Timing of Hypersensitivity Reactions in Relation to Dose

| Onset in relation to dose | **Motavizumab N=3320** | **Palivizumab N=3298** |
|---|---|---|
| Dose 1 | 5/38 (13%) | 1/13 (8%) |
| Dose 2 | 12/38 (32%) | 5/13 (38%) |
| Dose 3 | 6/38 (16%) | 0 |
| Dose 4 | 8/38 (21%) | 3/13 (23%) |
| Dose 5 | 7/38 (18%) | 4/13 (31%) |

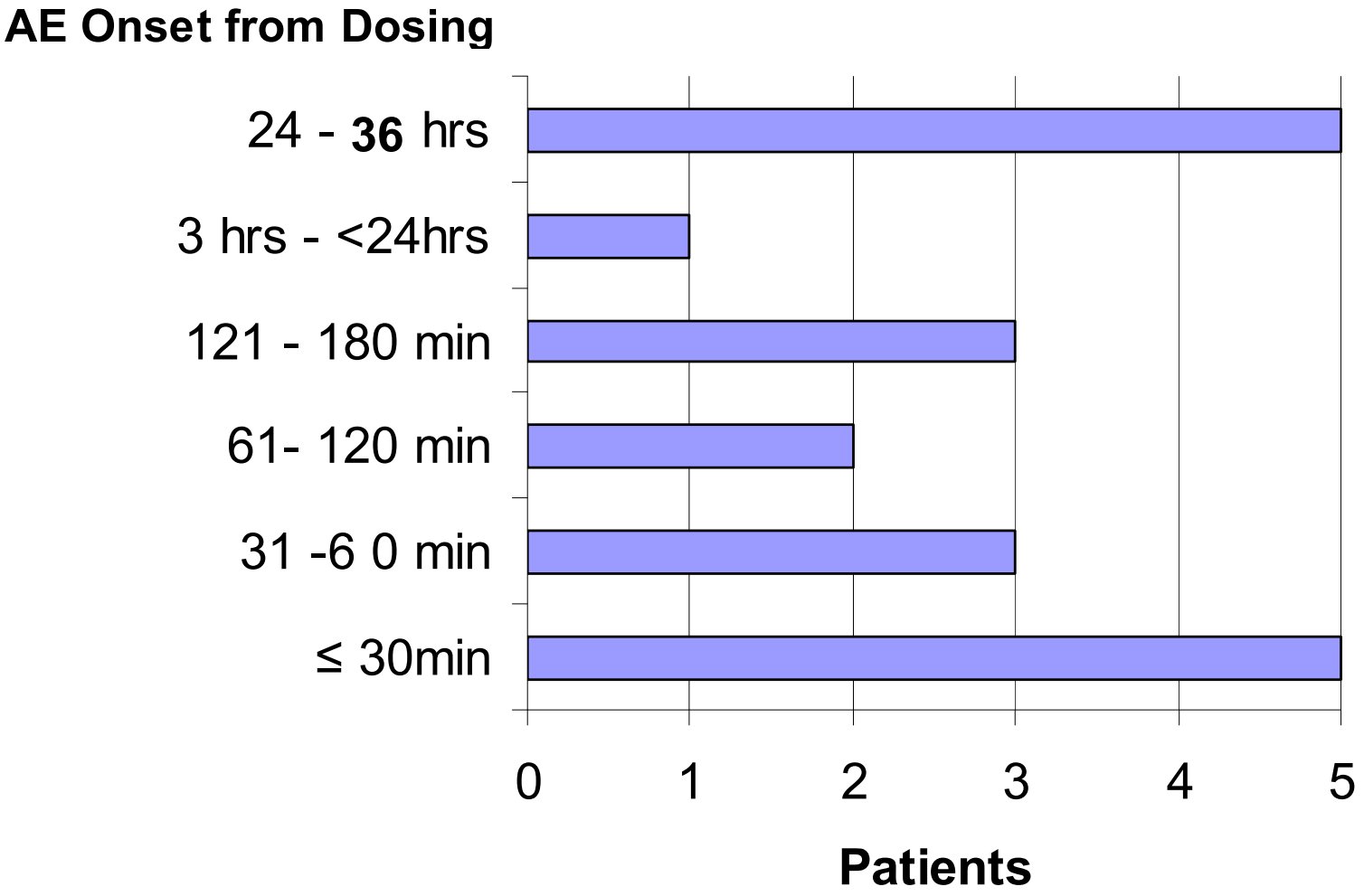
# High Grade Hypersensitivity Events

**Grade 3-4 or Serious Specific Skin/Hypersensitivity Event of Interest Occurring Within Two Days of Dosing**

| | Studies | | | | | |
|---|---|---|---|---|---|---|
| **Product** | **CP-110** | **CP-124** | **CP-117** | **CP-118** | **CP-127** | **TOTAL** |
| **Motavizumab** | **8** | **4*** | **5*** | **1*** | **1** | **19** |
| **Palivizumab** | **0** | **0** | **N/A** | **N/A** | **0** | **0** |

* One suggestive anaphylaxis case each in study CP-124, CP-117, CP-118

# Timing of High Grade Hypersensitivity Events for Motavizumab



# Anaphylaxis Definition

## Any one of the following 3 criteria:

1. Acute onset involving skin, mucosa or both

   AND at least one of the following:

   – a. respiratory compromise

   – b. decreased BP or end-organ dysfunction

2. Two or more that occur rapidly after exposure:

   – a. involvement of the skin-mucosal tissue

   – b. respiratory compromise

   – c. decreased BP or associated symptoms

   – d. persistent GI symptoms

3. Decreased BP after exposure to known allergen (minutes to several hours)

# Anaphylaxis

- NIAID/FAAN definition does not require presence of shock nor the administration of epinephrine or IV resuscitation to classify an event as anaphylaxis
- Anaphylaxis reactions can vary in severity from mild to cardiovascular shock
- **Anaphylaxis is potentially life-threatening by virtue of the multisystem involvement and inherent unpredictability**
  - natural course of anaphylaxis is not fully understood

# FDA's Analysis of Cases Suggestive of Anaphylaxis

# Case #1: CP-118

16 m.o., 34-week g.a., Hispanic female; h/o atopic dermatitis.

Tolerated first two doses of motavizumab

- 15 minutes after her third dose of motavizumab, developed a dry cough (without stridor or difficulty breathing), periorbital erythema, lesions on back and neck (without pruritus), and mild palpebral edema
- Blood pressure dropped from 121/72 pre-dose to 75/50, 30 minutes post-dose. No prior hypotension with doses 1 and 2. Child had systolic BP > 100 mg Hg with prior study visit measurements.
- Treated with anti-histamine. Approximately 15 minutes later, the patient's cough and palpebral edema and some skin lesions decreased; new lesions around nose and mouth.
- Given 10 mg oral prednisone; 30 minutes later, decreased facial lesions with continued improvement.
- Event resolved the same day. Sent home on a 5-day treatment of oral anti-histamine and prednisone. Investigator coded AE as Grade 4 – life threatening.

# Case #2 CP-124

14m.o. Eastern Europe female; 42 weeks g.a. with ASD, bilateral OM, weight < 10th percentile; no previous h/o of drug allergies

- One hour after 5th motavizumab dose, developed severe urticaria on her face, torso, and legs, with edema on cheeks and hoarseness. Vital signs remained normal.
- Given hydrocortisone IV, followed by oral anti-histamine and oral calcium
- 2.5 hrs after dose, urticaria and edema on the cheeks had disappeared. Observed for two hours and subsequently released home in good condition.
- Investigator assessed this event as Grade 3 hypersensitivity

# Case #3 CP-117

6.2 month old Native American female with a history of reactive airways disease/asthma and an erythematous maculopapular rash

- Within an hour following dose 5, patient experienced swelling of eyes, face and fingers; erythema of the face and arms; and mild wheezing in the right upper lobe
- Treated with Benadryl IM and solumedrol; albuterol and inhaled steroids
- Event resolved the same day
- Investigator assessed this event as Grade 3 hypersensitivity

# Additional Motavizumab Grade 3 Events of Concern

- CP-110: One Grade 3 urticarial event
  - tachycardia (153→192)
- CP-117: One Grade 3 (SAE) hypersensitivity/urticarial event
  - tachycardia (152→186)
  - tachypnea (36→48)

- Note: BP not recorded in CP-110 & CP-117 since not required in protocol

# Motavizumab Anti-Drug Antibodies (ADA) and Skin/Hypersensitivity Reactions

| | ADA to Motavizumab | | |
|---|---|---|---|
| | Not Detected N=4137 | Detected N=75 (1.8%) | RR of Skin/HS Rxn in ADA+ |
| Skin/HS Events of Interest | 295 (7.1%) | 23 (30.7%) | 4.3 |
| ▪ ≥Grade 3 AE or SAE | 15 ( 0.4%) | 8 (10.7%) | 26.8 |
| ▪ AE D/C | 4 ( 0.1%) | 6 ( 8.0%) | 80 |
| ▪AE ≤ 2d After Dosing | 20 ( 0.5%) | 10 (13.3%) | 26.6 |

**No association found for palivizumab ADA and skin/hypersensitivity reactions**

# Safety Summary

- The overall safety profiles of motavizumab and palivizumab were similar in CP-110 and CP-124
- However, motavizumab had an increased frequency of hypersensitivity reactions compared to palivizumab, including cases suggestive of anaphylaxis
- Safety data from CP-117 only reflects AE profile of motavizumab in Native Americans

# Safety Summary (cont.)

- Motavizumab has 3 cases/5360 patients exposed suggestive of anaphylaxis with a potential rate of 56/100,000 patients exposed

- Motavizumab had at least a three-fold increase in severe skin/hypersensitivity reactions compared to palivizumab

- In CP-110 the majority of study-related discontinuations for motavizumab were due to hypersensitivity reactions
  - no hypersensitivity-related discontinuations for palivizumab

# Safety Summary (cont.)

- No cases of anaphylaxis in original palivizumab data base and in the motavizumab development program in patients who received palivizumab
- In 12 years since approval, experts estimate there were approximately 1.2 million patients dosed with palivizumab
- We have identified 10 post-marketing cases of anaphylaxis for palivizumab spontaneously reported to the AERS data base
  - AERS database not suitable for calculating AE incidence
- Warning for anaphylaxis appears in palivizumab label
- Palivizumab is commonly administered at home or in a clinic setting:
  - There have been studies of palivizumab to support the safety of home administration by health professionals

# Risk - Benefit

- Motavizumab has an increased frequency and greater severity of hypersensitivity reactions including at least three cases suggestive of anaphylaxis compared to palivizumab
- Motavizumab met the non-inferiority criteria for RSV hospitalizations in the primary analysis in CP-110 and was superior to placebo in CP-117
- However, there were limitations in CP-110:
  - Results sensitive to misclassification
  - Need to consider impact of local testing procedures