U.S. Food and Drug Administration

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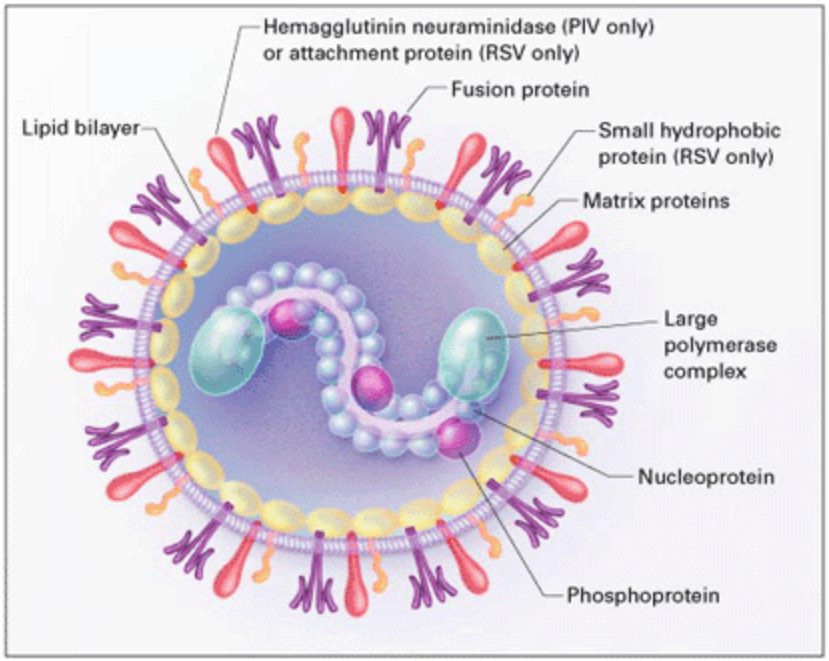
Motavizumab
BLA 125283

Antiviral Drugs Advisory Committee Meeting

June 2, 2010

Silver Spring, MD

RSV



- RSV is an enveloped RNA paramyxovirus virus lacking neuraminidase and hemagglutinin surface glycoproteins
- Causes acute respiratory tract illness in all ages
- Most important cause of bronchiolitis and pneumonia in infants and young children

Hall, NEJM, 2001

RSV Infections

- Characteristics that increase the risk of severe or fatal RSV infection in children include:
  - Prematurity
  - Cyanotic or complicated congenital heart disease (CHD)
  - Chronic lung disease (CLD) of prematurity
  - Immunodeficiency
  - Therapy causing immunosuppression

Regulatory History: Palivizumab

- Palivizumab (Synagis®) is a monoclonal antibody directed against the F protein of RSV
- Initially approved for passive immunoprophylaxis in 1998 at a dose of 15 mg/kg IM q monthly for 5 doses during RSV season
  - Indicated for prevention of RSV in premature infants, < 35 weeks gestation with CLD of prematurity (study 018)
  - Subsequently approved for use in children with hemodynamically significant CHD (study 048)

Motavizumab

- Humanized monoclonal antibody derived from its approved parent monoclonal antibody palivizumab (Synagis®) for passive immunoprophylaxis against RSV
  - 15 mg/kg IM
  - Directed against RSV F protein
- Differs from palivizumab by 13 amino acid residues
  - increased binding avidity with enhanced *in vitro* neutralizing activity relative to palivizumab

Regulatory History: Motavizumab

- October 2003 - initial dose-finding in adults; subsequently four additional Phase 1 / 2 studies conducted
- Fall 2004 - CP110 initiated
- May 2005 - formal EOP2 meeting
- MedImmune enrolls patients with hemodynamically significant congenital heart disease in a separate study (study CP124)
- 2007 pre-BLA meeting

Motavizumab BLA

- Planned original BLA submission to contain a single large Phase 3 trial comparing motavizumab to palivizumab – CP 110
  - Primary endpoint was prevention of RSV hospitalization
- Non-inferiority margin based on palivizumab trial 018
  - Differences between 018 population and CP 110 population wrt hospitalization rates, proportion of subjects with CLD, patients < 32 weeks g.a. and a different geographic site selection
    - Native American study CP-117 was used as a supportive study although it was recognized that subjects enrolled in CP-117 were healthy, full term infants previously recognized to be at high risk of serious RSV disease compared to other healthy full term infants

Regulatory History: Motavizumab

- Initial BLA Submission January 2008
- Initial Action: Complete Response letter sent November 2008
  - CR letter is a more consistent and neutral mechanism to convey that FDA cannot approve an application in its present form
  - Unable to complete review without additional data
  - MedImmune's reply to CR letter received December 2009
- Antiviral Drugs Advisory Committee Meeting June 2, 2010

CR Letter Issues: November 2008

- The decision to admit patients was not performed solely on clinical grounds, but could have included the use of local RSV testing
  - Local testing not uniformly applied
  - Could this practice impact hospitalization?
- The study medications appeared to interfere with some licensed local RSV assays
- Some centrally used real-time RT-PCR results were discordant with local RSV assay results

CR Letter Issues (cont)

- Requested a chart review for studies CP110 and CP117
  - In subjects presenting with respiratory tract infection
  - Local test results
  - Testing methodologies to ascertain if there was interference by study medications

CR Letter Issues (cont)

- Increased number of patient deaths and apparent life-threatening events (ALTEs) among motavizumab recipients compared to either palivizumab or placebo
- There appeared to be an imbalance in the incidence of specific categories of neurologic adverse events including serious adverse events between motavizumab and palivizumab or placebo.
- In the phase 3 studies, testing for anti-motavizumab antibodies was performed at a time when remaining circulating motavizumab was likely to have affected the results.

CR Letter Issues (cont)

- There appeared to be a link between the development of anti-drug antibodies (ADA) and the occurrence of hypersensitivity reactions, post dosing.

- Applicant submitted a complete response in December 2009
  - Additional study in CHD patients (CP-124)
  - Enabled FDA to continue the BLA review to make a risk/benefit determination

Questions

- Please comment on the **safety** profile of motavizumab, specifically with respect to the potential for hypersensitivity reactions, including anaphylaxis.

- Do the data from the applicant's studies adequately support the **efficacy** of motavizumab for the prevention of serious lower respiratory tract infection with RSV in at-risk infants?

- Given the potential benefits and risks, should motavizumab be licensed for marketing? Please discuss. Vote: Yes/No

  – If no, what additional data/studies can be provided to support the licensing of motavizumab? If yes, are there post-marketing studies needed to a) provide additional safety data or b) optimize use of motavizumab?

Meeting Goals

Can we conclude that the benefits are greater than the risks for motavizumab for the following proposed indication:

for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease?

Agenda

8:00 am – 8:10 am	**Call to Order and Opening Remarks** **Craig Hendrix, MD** **Acting Chair, Antiviral Drugs Advisory committee** **Introduction of Committee**
8:10 am - 8:15 am	**Conflict of Interest Statement** **Designated Federal Officer**
8:15am	**FDA Introductory Remarks** **Debra Birnkrant, MD** **Director, Division of Antiviral Products**
8:30 am – 10:00 am	**Presentations by MedImmune**
10:00 am	**Clarification/questions**
10:15 am	**BREAK**
10:30 - 11:15 am	**FDA PRESENTATION** **Clinical Efficacy and Safety** **Alan Shapiro, MD, Ph.D.** **Medical Officer** **Division of Antiviral Products**
11:15 - noon	**Clarification/questions for FDA and Applicant**
12:00 pm	**LUNCH**
1:00pm	**Open Public Hearing**
2:00 pm	**Charge to the Committee - Discussion/questions**
5:00 pm	**Adjournment**