FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Introductory Remarks

New Drug Application (NDA) 202049: Dry powder mannitol (DPM) for inhalation for the management of cystic fibrosis (CF) to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies

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Cystic Fibrosis

- Autosomal recessive disorder
  - Mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene
  - Affects ~30,000 people in U.S.
- Multi-system disease
  - Airway obstruction, infection
  - Exocrine pancreatic insufficiency
  - Gastrointestinal abnormalities
  - Reproductive abnormalities
- Therapies
  - Symptomatic and complications of disease
  - CFTR “modulators” (first approval 2012)
- Remains a need for additional therapies

Dry Powder Mannitol (DPM) for Inhalation

- Sugar alcohol
  - Generally recognized as safe by enteral route
  - Approved as a bronchoprovocation agent by inhaled route (Aridol)
- Proposed indication
  - Management of CF to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies
- Dose: 400mg (10 capsules) by inhalation twice daily
- Initial NDA submitted May 2012 – Complete Response (CR)
- Current submission – Response to CR

Original NDA Submission

- Single dose-ranging study (202)
- Two 26-week phase 3 studies in CF patients ≥ 6 years
  - Studies 301 and 302
  - Primary endpoint – change from baseline in forced expiratory volume in one second (FEV_1) over 26-weeks
  - Secondary endpoints – included exacerbation and Cystic Fibrosis Questionnaire – Revised respiratory domain (CFQ-RRD) score
  - If a patient discontinued treatment, there were no provisions to continue following the patient

Original NDA Submission - Key Findings

- Efficacy –
  - Study 301 – positive FEV_1 results, but not statistically robust due to significant issues with differential drop-out and missing data.
    - 37% of DPM and 27% of control patients discontinued treatment
  - Study 302 – not statistically significant for primary endpoint
  - No support from secondary endpoints
- Safety –
  - Hemoptysis particularly in pediatric population

Complete Response (CR)

- January 2013 PADAC meeting
  - Unanimously voted against approval
- CR deficiency
  - Efficacy – not adequately demonstrated
  - Safety – hemoptysis safety concern primarily in pediatrics
- To address deficiency
  - Conduct at least one additional clinical trial to show substantial evidence of efficacy and balancing safety findings

Current Submission

- Indication limited to adults
- New 26-week phase 3 study in ≥ 18 years of age (303)
  - Primary endpoint – same as 301 and 302
  - Secondary endpoints – included exacerbation and symptoms
  - Designed to address concerns raised in Studies 301 and 302
  - Limited population to ≥ 18 years due to hemoptysis safety concerns
- *Post-hoc* analyses of ≥ 18 years of age subgroup from Studies 301 and 302
  - *Post-hoc* analyses same issues as in original submission

Efficacy Summary ≥18 years

- Change from baseline in FEV_1 over 26-weeks
  - Study 303
    - Statistically significant at approximately 50mL
  - *Post-hoc* analyses of Studies 301 and 302
    - Point estimates of approximately 80mL
- Exacerbation
  - No statistically significant differences
  - Study 303 – favored control (rate)
  - Study 302 – *post-hoc* analysis favored control (rate)
  - Study 301 – *post-hoc* analysis favored DPM (rate)
- CFQ-R respiratory domain score
  - No statistically significant differences

Efficacy Considerations

- Only Study 303 demonstrated clear statistically significant improvements in FEV_1
- Studies 301 and 302 analyses in ≥18 year olds were ***post-hoc***
  - Study 301 FEV1 result not statistically robust
  - Study 302 did not "win" on FEV_1
- FEV_1 effect size modest across studies - Clinically meaningful?
- Clinically important secondary endpoints across all studies not supportive of efficacy

Topics for Discussion

- Efficacy
  - Is there substantial evidence of efficacy in patients ≥18 years?
    - FEV_1 effect size modest
    - No secondary endpoint support
    - Statistical persuasiveness
- Safety
  - Exacerbation
  - Hemoptysis


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