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 FEV₁ 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
  – Hemoptyis
FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Overview of Clinical Program

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

Khalid Puthawala, MD
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Center for Drug Evaluation and Research
US Food and Drug Administration
FDA Presentation Outline

• Overview of Clinical Program
  – Khalid Puthawala, MD, Clinical Reviewer

• Statistical Review of Efficacy
  – Cesar Torres, PhD, Statistical Reviewer

• Clinical Review of Efficacy, Safety, and Benefit-Risk Assessment
  – Khalid Puthawala, MD, Clinical Reviewer
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# CF Therapies

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active ingredient</th>
<th>FDA approved for CF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucolytics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmozyme</td>
<td>Dornase (nebulized)</td>
<td>Yes</td>
</tr>
<tr>
<td>---</td>
<td>Hypertonic saline (nebulized)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pro-Air, Ventolin, Proventil</td>
<td>Albuterol</td>
<td>Approved as bronchodilator</td>
</tr>
<tr>
<td><strong>Inhaled Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOBI</td>
<td>Tobramycin (nebulized)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cayston</td>
<td>Aztreonam (nebulized)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cystic Fibrosis Transmembrane Receptor (CFTR) modulators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalydeco</td>
<td>Ivacaftor</td>
<td>Yes, mutation specific</td>
</tr>
<tr>
<td>Orkambi</td>
<td>Lumacaftor/Ivacaftor</td>
<td>Yes, mutation specific</td>
</tr>
<tr>
<td>Symdeko</td>
<td>Tezacaftor/Ivacaftor</td>
<td>Yes, mutation specific</td>
</tr>
</tbody>
</table>
Recent CF approvals

• Primary endpoint
  – $\text{FEV}_1$: improvement of $\sim 3\%$ to $13\%$ predicted

• Secondary endpoints
  – Included exacerbation measures, Cystic Fibrosis Questionnaire – Revised respiratory domain score (CFQ-RRD), Body Mass Index (BMI)
  – General support
DPM for CF: Regulatory History

• Original NDA submission - May 2012
  – Efficacy and safety concerns
• AC meeting - Jan 2013
  – Unanimous vote against approval
• CR action - Mar 2013
  – Need additional trial: substantial efficacy and balanced safety
• Current submission - Dec 2018
Original Submission Issues

• Two phase 3 studies: studies 301 and 302

• Efficacy issues
  – Study 301: significant statistical issues due to large amount of disproportionate dropouts, 37% DPM vs. 27% control
  – Study 302: no statistical “win” on primary endpoint
  – Small FEV$_1$ treatment effect, clinically meaningful?
  – No secondary endpoint support

• Safety concern: hemoptysis
  – Especially in younger patients
Advisory Committee: 2013

• Voting
  – Adequate Benefit-Risk profile? No: 14, Yes: 0
    • Effective? No: 11, Yes: 3
    • Safe? No: 11, Yes: 3

• Comments
  – Adult population vs. Younger population
Complete Response (CR)

• CR - March 2013
  – Deficiencies:
    • Inadequate demonstration of efficacy: treatment-related dropouts, lack of statistical significance, no secondary support
    • Safety concerns of hemoptysis raised in younger patients
    • Overall, benefit-risk not balanced
  – Recommend:
    • ≥ 1 future trial with substantial evidence of efficacy
    • Address safety concerns including hemoptysis
    • Adults only
Regulatory History: Post-CR

• Type A meeting - May 2013
  – Identical design may be expedient
    • Minimize missing data/ drop-out
  – Exclude younger patients due to safety concerns
  – FEV₁ over 6 months acceptable but must be statistically significant and clinically convincing
  – Exacerbations important, must trend favorably
  – “Tie breaker” trial (study 303)

• Pre-NDA meeting - Nov 2016
  – Exacerbations, CFQ-RRD important secondary endpoints
  – Analysis of FEV₁ at 26 weeks important (primary endpoint: FEV₁ over 26 weeks)
Current Submission: Clinical Program

• Original submission
  – Five phase 1 and 2 studies
    • Majority open-label
  – Pivotal Dose ranging: Study 202
    • Open-label, cross-over, 2 week, 48 patients
    • 400mg twice daily dose for phase 3
    • 40mg dose no effect → 50mg twice daily control

• Current submission
  – Three phase 3 studies: Studies 301, 302, 303
    • Studies 301 and 302, post-hoc analysis of adults only

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# Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Treatment</th>
<th>N**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF-301</td>
<td>26 weeks</td>
<td>DPM 400 mg BID Control (DPM 50 mg BID)</td>
<td>177/118</td>
</tr>
<tr>
<td>CF-302</td>
<td>26 weeks</td>
<td>DPM 400 mg BID Control (DPM 50 mg BID)</td>
<td>184/121</td>
</tr>
<tr>
<td>CF-303</td>
<td>26 weeks</td>
<td>DPM 400 mg BID Control (DPM 50 mg BID)</td>
<td>209/214</td>
</tr>
</tbody>
</table>

*Study patients could not use hypertonic saline or have recent hemoptysis (>60mL within 3 months)

** For studies 301 and 302, N values shown represent all patients age 6 and older
## Phase 3 Studies: Key Differences

<table>
<thead>
<tr>
<th>Study</th>
<th>Years conducted</th>
<th>Design</th>
<th>Age groups</th>
<th>US patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF-301</td>
<td>(2007-2010)</td>
<td>No specific provision to follow patients after treatment discontinuation</td>
<td>Ages ≥ 6 years old (<em>Post-hoc</em> adult efficacy analysis)</td>
<td>No US patients</td>
</tr>
<tr>
<td>CF-302</td>
<td>(2008-2010)</td>
<td>No specific provision to follow patients after treatment discontinuation</td>
<td>Ages ≥ 6 years old (<em>Post-hoc</em> adult efficacy analysis)</td>
<td>US patients included</td>
</tr>
<tr>
<td>CF-303</td>
<td>(2014-2017)</td>
<td>Specific provision to follow patients after treatment discontinuation</td>
<td>Adults only</td>
<td>US patients included</td>
</tr>
</tbody>
</table>
Study 303: Design

Screening
Mannitol Tolerance Test

26 week Double blind Treatment Phase:
DPM 400mg BID
Control BID

Assessments: PFTs, AE review, CM assessment, CFQ-RRD

Abbreviations: PFT – Pulmonary function test, AE – Adverse event, CM – Concomitant medication, CFQRRD – Cystic fibrosis questionnaire revised respiratory domain
Study 303: Efficacy Endpoints

• Primary: FEV$_1$ over 26 weeks
  – Identical to studies 301, 302

• Secondary:
  – Forced Vital Capacity (FVC)
  – Protocol-Defined Pulmonary Exacerbation (PDPE) endpoints:
    • Rate
    • Time to PDPE
    • Antibiotic use for PDPE
    • Hospitalization for PDPE
  – CFQ-RRD score
  – Study 301, 302 similar but not identical
Disposition: Study 303

- Study withdrawal balanced
- Treatment discontinuation without study withdrawal allowed
- Study withdrawal rates lower than studies 301 and 302
  - 301: 37% DPM, 27% control
  - 302: 17% DPM, 12% control

<table>
<thead>
<tr>
<th></th>
<th>DPM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>209</td>
<td>214</td>
</tr>
<tr>
<td>Completed study (%)</td>
<td>183 (88)</td>
<td>190 (89)</td>
</tr>
<tr>
<td>Early study withdrawal (%)</td>
<td>26 (12)</td>
<td>24 (11)</td>
</tr>
<tr>
<td>Early treatment discontinuation (%)</td>
<td>37 (18)</td>
<td>44 (21)</td>
</tr>
</tbody>
</table>
**Demographics: Study 303**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>DPM (N=209)</th>
<th>Control (N=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>26.8 (8)</td>
<td>28.6 (11)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>92 (44)</td>
<td>107 (50)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>202 (97)</td>
<td>209 (98)</td>
</tr>
<tr>
<td>United States (%)</td>
<td>57 (27)</td>
<td>59 (28)</td>
</tr>
<tr>
<td>Disease Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hemoptysis (%)</td>
<td>68 (33)</td>
<td>60 (28)</td>
</tr>
<tr>
<td>Mean FEV$_1$ % predicted</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>At least one <em>F508del mutation</em> (%)</td>
<td>146 (70)</td>
<td>137 (64)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em>, mucoid (%)</td>
<td>66 (32)</td>
<td>62 (29)</td>
</tr>
</tbody>
</table>
FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Statistical Review of Efficacy

Cesar Torres, PhD
Division of Biometrics II
Office of Biostatistics
Center for Drug Evaluation and Research
US Food and Drug Administration
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Outline

• Study 303 endpoints and analysis
  – Key differences from Studies 301 and 302

• Results
  – Primary endpoint – $\text{FEV}_1$
  – Secondary endpoints
  – Regional subgroup analyses
Study 303 Primary Endpoint

• Change from baseline over 26 weeks in Forced Expiratory Volume in 1 Second (FEV₁)
  – Model included assessments at Weeks 6, 14, 26. Change from baseline to each visit was given equal weight.
Study 303 Primary Endpoint
Applicant’s Primary Analysis

• Model used:
  – Mixed Effects Model for Repeated Measures (MMRM)
  – Adjusting for treatment, rhDNase use, pooled country (US vs non-US), visit, interaction term between treatment and visit, baseline FEV$_1$, and baseline percent predicted FEV$_1$

Abbreviation: rhDNase-recombinant human deoxyribonuclease
Study 303 Primary Endpoint
Applicant’s Primary Analysis

• Missing data handling:
  – All observed data used, even that collected after treatment discontinuation
  – Used modified Baseline Observation Carried Forward (BOCF)
    • BOCF for those who withdrew from the study due to
      – AE
      – Death
      – Physician decision
      – Lack of efficacy
    – No imputation for those who withdrew for other reasons
Studies 301 and 302 Primary Endpoint
Applicant’s Primary Analysis

• Missing data handling:
  – No imputation for those who withdrew for any reason
Study 303 Secondary Endpoints

• Hierarchical
  – Change from Baseline Over 26 weeks in Forced Vital Capacity (FVC)
  – Time to First Protocol Defined Pulmonary Exacerbation (PDPE)
  – Number of Days on Antibiotics Due to PDPE
  – Number of Days in Hospital Due to PDPE
  – Rate of PDPE

• Non-Hierarchical
  – Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-RRD)
Study 303 Analyses of Secondary Endpoints

• Change from Baseline in FVC Over 26 Weeks
  – Primary analysis same as for primary endpoint

• Time to First PDPE
  – Cox Proportional Hazards Model

• Antibiotics, Hospitalizations, and PDPE Rate
  – Negative Binomial Model
Handling of Patient Withdrawal for PDPE Rate Endpoint

• Study 303
  – For each patient who withdrew before Week 26 with no observed instances of a PDPE, the number of PDPEs was imputed using that patient’s pulmonary exacerbation count in previous 12 months

• Studies 301 and 302
  – No imputation was prespecified
FDA ANALYSIS RESULTS
## Study 303: Primary Endpoint

### Primary Analysis: BOCF Using Dropout Reasons

<table>
<thead>
<tr>
<th>Change from baseline in FEV$_{1}$ over 26 weeks (weeks 6, 14, and 26)</th>
<th>DPM (N=209)</th>
<th>Control (N=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean change from baseline</td>
<td>65 mL</td>
<td>10 mL</td>
</tr>
<tr>
<td>Adjusted mean difference (95% CI) p-value</td>
<td>55 mL (9 to 101 mL) p = 0.018</td>
<td></td>
</tr>
</tbody>
</table>
### Study 303: Primary Endpoint
Sensitivity Analysis: Pattern Mixture Model

<table>
<thead>
<tr>
<th>Change from baseline in FEV\textsubscript{1} over 26 weeks (weeks 6, 14, and 26)</th>
<th>DPM (N=209)</th>
<th>Control (N=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean change from baseline</td>
<td>63 mL</td>
<td>12 mL</td>
</tr>
<tr>
<td>Adjusted mean difference (95% CI) p-value</td>
<td>51 mL (6 to 97 mL) p = 0.028</td>
<td></td>
</tr>
</tbody>
</table>

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Study 303 By-Arm Data Missingness Rates

- **DPM**
- **Control**
- **Study 303**

**Graph Details:**
- **X-axis:** Week
- **Y-axis:** Missingness
- **Missingness Levels:** 0%, 10%, 20%, 30%, 40%
By-Study By-Arm Data Missingness Rates

![Graph showing data missingness rates over time for different studies and conditions.](image-url)
By-Study PMM Analysis Results (Adults Only)

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Studies 301 and 302 is limited.

Abbreviation: PMM-Pattern Mixture Model

---

<table>
<thead>
<tr>
<th>Study</th>
<th>Change from Baseline in FEV₁ Over 26 Weeks, in mL</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>78 mL (95% CI: 21 to 135)</td>
<td>209</td>
</tr>
<tr>
<td>302</td>
<td>78 mL (95% CI: 2 to 153)</td>
<td>157</td>
</tr>
<tr>
<td>303</td>
<td>51 mL (95% CI: 6 to 97)</td>
<td>423</td>
</tr>
</tbody>
</table>
Change from Baseline in FEV$_1$ Over Time: Study 303

60 mL (11 to 109) 56 mL (2 to 109) 39 mL (-18 to 96)

*Figure includes by-arm point estimates and 95% confidence intervals.
# Secondary Endpoints: Study 303

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DPM (N = 209)</th>
<th>Control (N = 214)</th>
<th>Difference or Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>26 mL</td>
<td>-10 mL</td>
<td>AMD: 36 mL</td>
<td>-15 to 87</td>
<td>0.169</td>
</tr>
<tr>
<td>Time to 1\textsuperscript{st} PDPE</td>
<td></td>
<td></td>
<td>AHR: 1.14</td>
<td>0.67 to 1.94</td>
<td></td>
</tr>
<tr>
<td>Days on Antibiotics</td>
<td>6.0</td>
<td>7.9</td>
<td>ARR: 0.75</td>
<td>0.20 to 2.85</td>
<td></td>
</tr>
<tr>
<td>Days in Hospital</td>
<td>1.2</td>
<td>0.9</td>
<td>ARR: 1.27</td>
<td>0.32 to 5.15</td>
<td></td>
</tr>
<tr>
<td>PDPE Rate (per patient per year)</td>
<td>0.349</td>
<td>0.226</td>
<td>ARR: 1.55</td>
<td>0.99 to 2.41</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMD-adjusted mean difference, AHR-adjusted hazard ratio, ARR-adjusted rate ratio

Not Reported
By-Study PDPE Rate (Adults Only)

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Studies 301 and 302 is limited.

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By-Study PDPE Rate (Adults Only)

0.77 (95% CI: 0.47 to 1.26) N = 190

1.35 (95% CI: 0.56 to 3.24) N = 151

1.55 (95% CI: 0.99 to 2.41) N = 423

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Studies 301 and 302 is limited.
Secondary Endpoints: Study 303

• Cystic Fibrosis Questionnaire-Revised Respiratory Domain
  – Primary analysis same as for primary endpoint
  – Treatment effect difference: 0.87 (95% CI: -1.4 to 3.1) p=0.53
  – Results are consistent with those from Studies 301 and 302
US VS NON-US RESULTS
By-Study By-Region PMM Analysis Results (Adults Only)

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Study 302 is limited.

Change from Baseline in FEV₁ Over 26 Weeks, in mL

- Study 302:
  - US: 84 mL (95% CI: -1 to 169)  N = 93
  - Non-US: 68 mL (95% CI: -69 to 206)  N = 64

- Study 303:
  - US: 68 mL (95% CI: -21 to 156)  N = 116
  - Non-US: 50 mL (95% CI: -3 to 104)  N = 307
### Secondary Endpoints: Studies 303 by Region

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>US</th>
<th>Non-US</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM N = 57</td>
<td>Control N = 59</td>
<td>DPM N = 152</td>
</tr>
<tr>
<td>Time to First PDPE, AHR</td>
<td>2.02</td>
<td>0.87</td>
<td>1.14</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.78 to 5.22</td>
<td>0.46 to 1.66</td>
<td>0.67 to 1.94</td>
</tr>
<tr>
<td>Days on Antibiotics, ARR</td>
<td>0.96</td>
<td>0.70</td>
<td>0.75</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.09 to 10.51</td>
<td>0.15 to 3.09</td>
<td>0.20 to 2.85</td>
</tr>
<tr>
<td>Days in Hospital, ARR</td>
<td>1.39</td>
<td>1.24</td>
<td>1.27</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.10 to 18.67</td>
<td>0.27 to 5.78</td>
<td>0.32 to 5.15</td>
</tr>
</tbody>
</table>

Abbreviations: AHR-Adjusted Hazard Ratio, ARR-Adjusted Rate Ratio
By-Study By-Region PDPE Rate (Adults Only)

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Study 302 is limited.*

- Study 302:
  - US: 1.48 (95% CI: 0.53 to 4.14) N = 88
  - Non-US: 1.04 (95% CI: 0.20 to 5.54) N = 63

- Study 303:
  - US: 2.93 (95% CI: 1.36 to 6.32) N = 116
  - Non-US: 1.06 (95% CI: 0.61 to 1.86) N = 306
Summary

• Statistically significant results were observed when analyzing the primary efficacy endpoint for Study 303. These results appear to be statistically robust. However, the observed effect size is marginal.

• The interpretability of results from adult data in Studies 301 and 302 is limited due to issues previously raised, as well as the fact that the analyses are post-hoc.

• There is no support from secondary endpoints.
FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Clinical Review of Efficacy, Safety, and Benefit-Risk Assessment

Khalid Puthawala, MD
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
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• Clinical Review of Efficacy, Safety, and Benefit-Risk Assessment
  – Khalid Puthawala, MD, Clinical Reviewer
Outline

• Efficacy Summary
  – Clinical context

• Safety
  – Exposure
  – Main safety results
    • Deaths
    • Serious non-fatal adverse events (SAEs)
    • Adverse events (AEs) leading to treatment discontinuation
    • Common AEs
    • AEs of special interest
  – Summary

• Benefit/Risk
By-Study PMM Analysis Results (Adults Only)

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Studies 301 and 302 is limited.

<table>
<thead>
<tr>
<th>Study</th>
<th>Change from Baseline in FEV₁ Over 26 Weeks, in mL</th>
<th>95% CI</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>78 mL</td>
<td>21 to 135</td>
<td>209</td>
</tr>
<tr>
<td>302</td>
<td>78 mL</td>
<td>2 to 153</td>
<td>157</td>
</tr>
<tr>
<td>303</td>
<td>51 mL</td>
<td>6 to 97</td>
<td>423</td>
</tr>
</tbody>
</table>

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Change from Baseline in FEV<sub>1</sub> Over Time: Study 303

*Figure includes by-arm point estimates and 95% confidence intervals.*
Clinical Perspective: $\text{FEV}_1$

- $\text{FEV}_1$
  - Measure of overall pulmonary function
  - Used as primary endpoint for many approved CF treatments
    - Prior approvals $\text{FEV}_1$ improvement ~ 3-13% predicted

- DPM
  - Not a bronchodilator: facilitates pulmonary toilet
  - Additional support beyond $\text{FEV}_1$
    - Exacerbations, infections, hospitalizations, symptoms

- DPM Phase 3 studies
  - $\text{FEV}_1$ treatment effect size small
  - Potential attenuation at 26 weeks: expected chronic use
# Secondary Endpoints: Study 303

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DPM (N = 209)</th>
<th>Control (N = 214)</th>
<th>Difference or Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>26 mL</td>
<td>-10 mL</td>
<td>AMD: 36 mL</td>
<td>-15 to 87</td>
<td>0.169</td>
</tr>
<tr>
<td>Time to 1&lt;sup&gt;st&lt;/sup&gt; PDPE</td>
<td>6.0</td>
<td>7.9</td>
<td>AHR: 1.14</td>
<td>0.67 to 1.94</td>
<td></td>
</tr>
<tr>
<td>Days on Antibiotics</td>
<td>1.2</td>
<td>0.9</td>
<td>ARR: 0.75</td>
<td>0.20 to 2.85</td>
<td></td>
</tr>
<tr>
<td>Days in Hospital</td>
<td>0.349</td>
<td>0.226</td>
<td>ARR: 1.55</td>
<td>0.99 to 2.41</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AMD adjusted mean difference, AHR adjusted hazard ratio, ARR adjusted rate ratio

Not Reported: Days on Antibiotics

FVC: Forced Vital Capacity
By-Study PDPE Rate (Adults Only)

- Study 301: 0.77 (95% CI: 0.47 to 1.26) N = 190
- Study 302: 1.35 (95% CI: 0.56 to 3.24) N = 151
- Study 303: 1.55 (95% CI: 0.99 to 2.41) N = 423

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Studies 301 and 302 is limited.*
By-Study By-Region PDPE Rate (Adults Only)

1.48 (95% CI: 0.53 to 4.14)  N = 88
1.04 (95% CI: 0.20 to 5.54)  N = 63
2.93 (95% CI: 1.36 to 6.32)  N = 116
1.06 (95% CI: 0.61 to 1.86)  N = 306

*The dashed and solid black lines for the confidence intervals are to visually indicate that the ability to compare results from Study 303 to those of Study 302 is limited.
Clinical Perspective: Secondary Endpoints

- Exacerbation measures
  - Large impact on CF patients quality of life
  - Used as secondary endpoints for approved CF treatments
    - 26 week duration: expectations
    - Expected trend towards improvement
  - DPM Phase 3 studies
    - Majority of point estimates do not favor DPM
    - US population: unfavorable results accentuated
- CFQ-RRD: no significant change
Clinical Perspective: Efficacy Summary

• Primary Endpoint – FEV$_1$
  – Statistically significant difference present
  – Treatment effect small

• Secondary endpoints
  – No support in entire phase 3 program
  – Exacerbations: unfavorable trend (studies 302 and 303)

• US subpopulation
  – Studies 302, 303: secondary endpoint trends accentuated
Outline

• Efficacy Summary
  – Clinical context

• Safety
  – Exposure
  – Main safety results
    • Deaths
    • Serious non-fatal adverse events (SAEs)
    • Adverse events (AEs) leading to treatment discontinuation
    • Common AEs
    • AEs of special interest
  – Summary

• Benefit/Risk
### Safety: Exposure

**Studies 301, 302, 303 pooled adult subgroup**

<table>
<thead>
<tr>
<th>Exposure (Months)</th>
<th>DPM (N=414)</th>
<th>Control (N=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>5.1 (2.1)</td>
<td>5.4 (1.8)</td>
</tr>
<tr>
<td><strong>Median (min, max)</strong></td>
<td>6 (0,7.8)</td>
<td>6 (0,7.8)</td>
</tr>
</tbody>
</table>

**Duration**

<table>
<thead>
<tr>
<th></th>
<th>DPM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>40 (9.7)</td>
<td>20 (5.8)</td>
</tr>
<tr>
<td>&gt;1-2</td>
<td>26 (6.3)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>&gt;2-3</td>
<td>12 (2.9)</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>&gt;3-4</td>
<td>14 (3.4)</td>
<td>19 (5.5)</td>
</tr>
<tr>
<td>&gt;4-5</td>
<td>6 (1.4)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>&gt;5-6</td>
<td>112 (27.1)</td>
<td>93 (26.8)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>204 (49.3)</td>
<td>186 (53.6)</td>
</tr>
</tbody>
</table>
## Safety: Overview

<table>
<thead>
<tr>
<th>Category</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=414)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
<tr>
<td>Patients with at least one SAE</td>
<td>78 (19)</td>
</tr>
<tr>
<td>Patients with any AE leading to treatment discontinuation</td>
<td>51 (12)</td>
</tr>
<tr>
<td>Patients with any AE leading to study withdrawal</td>
<td>40 (10)</td>
</tr>
<tr>
<td>Patients with at least one AE</td>
<td>321 (78)</td>
</tr>
</tbody>
</table>
# Safety: SAEs

<table>
<thead>
<tr>
<th>System Organ Class (SOC) / Preferred Term</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=414)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>78 (18.8)</td>
</tr>
<tr>
<td>General disorders</td>
<td>55 (13.3)</td>
</tr>
<tr>
<td>CF exacerbation (Condition aggravated)</td>
<td>55 (13.3)</td>
</tr>
<tr>
<td>Infection and Infestations SOC</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Respiratory SOC</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders SOC</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Procedures SOC</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

*Results shown for SOCs or PTs with ≥ 1% frequency*
### Safety: Treatment Discontinuation

<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=414)</td>
</tr>
<tr>
<td>Any TEAE leading to treatment discontinuation</td>
<td>51 (12.3)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal SOC</strong></td>
<td>35 (8.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (5.1)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>General disorder SOC</strong></td>
<td>18 (4.3)</td>
</tr>
<tr>
<td>CF exacerbation (Condition aggravated)</td>
<td>13 (3.1)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Infections SOC</strong></td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Psychiatric disorders SOC</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Nervous system disorders SOC</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

*Results shown for SOCs or PTs with ≥ 0.5% frequency

Abbreviations: TEAE – Treatment Emergent Adverse Event
# Safety: Treatment Discontinuation

<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
<th>DPM (N=414)</th>
<th>Control (N=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE leading to treatment discontinuation</td>
<td></td>
<td>51 (12.3)</td>
<td>30 (8.6)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal SOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>21 (5.1)</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Hemothysis</td>
<td></td>
<td>7 (1.7)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Wheezing</td>
<td></td>
<td>1 (0.2)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td><strong>General disorder SOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF exacerbation (Condition aggravated)</td>
<td></td>
<td>13 (3.1)</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td></td>
<td>4 (1)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td><strong>Infections SOC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders SOC</td>
<td></td>
<td>2 (0.5)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td><strong>Nervous system disorders SOC</strong></td>
<td></td>
<td>2 (0.5)</td>
<td>3 (0.9)</td>
</tr>
</tbody>
</table>

*Results shown for SOCs or PTs with ≥ 0.5% frequency*

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## Safety: All TEAEs

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=414)</td>
</tr>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>321 (77.5)</td>
</tr>
<tr>
<td>CF exacerbation (Condition aggravated)</td>
<td>132 (31.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>62 (15)</td>
</tr>
<tr>
<td>Headache</td>
<td>44 (10.6)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>43 (10.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (7.2)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Bacteria sputum identified</td>
<td>28 (6.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>23 (5.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 (4.6)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>18 (4.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23 (5.6)</td>
</tr>
</tbody>
</table>

*Results shown for PTs with ≥ 5% frequency or >2% difference between arms*
Safety: Special Concerns

• Original submission concern: Hemoptysis
• Current submission concern: Exacerbations
# Safety: Hemoptysis

<table>
<thead>
<tr>
<th>Hemoptysis</th>
<th>Study 301 and 302 pooled adults subgroup</th>
<th>Study 303</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=207)</td>
<td>Control (N=134)</td>
<td>DPM (N=207)</td>
</tr>
<tr>
<td>Any hemoptysis</td>
<td>22 (10.6)</td>
<td>11 (8.2)</td>
<td>21 (10.1)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>2 (1)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (2.4)</td>
<td>1 (0.7)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>AE leading to drug discontinuation</td>
<td>6 (2.9)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>AE leading to study withdrawal</td>
<td>6 (2.9)*</td>
<td>0*</td>
<td>0</td>
</tr>
</tbody>
</table>

*Treatment discontinuation led to study withdrawal

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## Safety: CF Exacerbations

<table>
<thead>
<tr>
<th>Category</th>
<th>Studies 301, 302, 303 pooled adults subgroup</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=414)</td>
<td>Control (N=347)</td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>55 (13.3)</td>
<td>39 (11.2)</td>
<td></td>
</tr>
<tr>
<td>AEs leading to drug discontinuation</td>
<td>13 (3.1)</td>
<td>9 (2.6)</td>
<td></td>
</tr>
<tr>
<td>AEs leading to study withdrawal*</td>
<td>11 (2.7)</td>
<td>5 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Severe AEs</td>
<td>20 (4.8)</td>
<td>10 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Any CF exacerbation</td>
<td>132 (31.9)</td>
<td>114 (32.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment discontinuation led to study withdrawal in studies 301, 302
<table>
<thead>
<tr>
<th>CF Exacerbations</th>
<th>Studies 301, 302, 303 Pooled adults subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U.S. Population</td>
</tr>
<tr>
<td></td>
<td>DPM (N=110)</td>
</tr>
<tr>
<td>SAEs</td>
<td>23 (20.9)</td>
</tr>
<tr>
<td>AEs leading to drug discontinuation</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>AEs leading to study withdrawal</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Any exacerbation</td>
<td>42 (23.8)</td>
</tr>
</tbody>
</table>
Safety Summary

• CF exac possible safety concern
  – More serious exacerbations, particularly in US population
  – More treatment discontinuations/study withdrawals
• Hemoptysis concern lessened by study 303 data
• Tolerability issue
  – Cough frequent, non-serious, but causing treatment withdrawal
  – Common AEs mostly related to airway effects
Efficacy Summary

FEV$_1$

- Change from Baseline in FEV$_1$ Over 26 Weeks, in mL
  - 78 mL (21 to 135mL)
  - 78 mL (2 to 153mL)
  - 51mL (6 to 97mL)

Exacerbation Rate

- PDPE Rate Ratio Over 26 Weeks
  - RR: 0.77 (0.47 to 1.26)
  - RR: 1.35 (0.56 to 3.24)
  - RR: 1.55 (0.99 to 2.41)
Benefit-Risk Assessment

- $\text{FEV}_1$: small treatment effect, unclear clinical significance
  - Original studies (301, 302): Post-hoc
    - Significant statistical problems
  - Current study (303): “won”
- Exacerbation endpoints: no support in any study
  - Unfavorable trends in two studies (302, 303)
  - US population worse
- Safety: Exacerbations
  - Slight increase in several safety categories
  - Serious exacerbations: US population worse
  - Consistent with efficacy results (PDPE rate increase, especially for US population)
FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
Charge to the Committee

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

Robert H. Lim, MD
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
Efficacy Considerations

- Only Study 303 demonstrated clear statistically significant improvements in FEV₁
- 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 FEV₁
- FEV₁ effect size small across studies - clinically meaningful?
- Clinically important secondary endpoints across all studies not supportive of efficacy
Safety Considerations

• Hemoptysis
• Exacerbation
Approval of an Application
21 CFR 314.105 (c)

• “FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.”
Efficacy Standard
21 CFR 314.125
Refusal to Approve an Application

• (b)(5) “...substantial evidence consisting of adequate and well-controlled investigations...that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”
Refusal to Approve an Application

(b)(2) “...do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”

(b)(3) “The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.”

(b)(4) “There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”
1. DISCUSSION: Discuss the efficacy of dry powder mannitol (DPM) for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. Include the following topics in your discussion:
   a) Effect on FEV$_1$, including effect size and durability of effect
   b) Secondary endpoints, particularly exacerbations and the Cystic Fibrosis Questionnaire – Revised respiratory domain score
   c) Statistical persuasiveness
2. **DISCUSSION**: Discuss the safety data for DPM for the proposed use in patients with cystic fibrosis 18 years of age and older, particularly exacerbation and hemoptysis.
Discussion Points and Voting Questions

3. **VOTE**: Do the data provide substantial evidence of efficacy for DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
   
   a) If no, what further data are needed?
4. **VOTE**: Are the safety data adequate to support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
   a) If no, what further data are needed?
Discussion Points and Voting Questions

5. VOTE: Does the benefit-risk profile support approval of DPM for the proposed indication of the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies?
   a) If no, what further data are needed?
Back-up Slides Shown
Analysis of PDPE Rate: Study 303

- For patients who withdrew before Week 26 with no observed instances of a PDPE:
  - Follow-up duration is imputed as 26 weeks
  - If a patient withdrew before Week 14, the number of PDPEs is imputed using half of the patient’s historical (previous 12 months) pulmonary exacerbation count rounded upwards
  - If a patient withdrew after Week 14, the number of PDPEs is imputed using one fourth of the patient’s historical (previous 12 months) pulmonary exacerbation count rounded upwards
### FEV₁ (mL) Tipping Point Analysis Results

<table>
<thead>
<tr>
<th>Shift for Control¹</th>
<th>-100</th>
<th>-50</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>40</td>
<td>44</td>
<td>47</td>
<td>51 L</td>
<td>55</td>
</tr>
<tr>
<td>p=0.093</td>
<td>(-7 to 87)</td>
<td>(-3 to 90)</td>
<td>(1 to 94)</td>
<td>(5 to 97)</td>
<td>(9 to 101)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shift for DPM¹</th>
<th>-50</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>51</td>
<td>54</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>p=0.051</td>
<td>(1 to 95)</td>
<td>(4 to 96)</td>
<td>(10 to 102)</td>
<td>(14 to 106)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shift for DPM¹</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>-50</td>
<td>55</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>p=0.023</td>
<td>(7 to 100)</td>
<td>(12 to 104)</td>
<td>(15 to 108)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Shift for DPM¹</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>57</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>p=0.015</td>
<td>(11 to 103)</td>
<td>(14 to 106)</td>
<td>(17 to 109)</td>
</tr>
</tbody>
</table>

1 Assumed difference in FEV₁ mean change from baseline over Week 26 between completers and dropouts. Mean changes in DPM/Control completers were 79/21 mL.
## By-Study Responder Analyses, Adults Only

<table>
<thead>
<tr>
<th>Study</th>
<th>Threshold</th>
<th>DPM</th>
<th>Control</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 301</td>
<td>N = 124</td>
<td>N = 85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mL</td>
<td>43 (34.7%)</td>
<td>20 (23.5%)</td>
<td>1.67 (0.89 to 3.20)</td>
</tr>
<tr>
<td></td>
<td>75 mL</td>
<td>40 (32.3%)</td>
<td>18 (21.2%)</td>
<td>1.71 (0.90 to 3.37)</td>
</tr>
<tr>
<td></td>
<td>100 mL</td>
<td>38 (30.6%)</td>
<td>17 (20.0%)</td>
<td>1.70 (0.88 to 3.40)</td>
</tr>
<tr>
<td>Study 302</td>
<td>N = 97</td>
<td>N = 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mL</td>
<td>39 (40.2%)</td>
<td>17 (28.3%)</td>
<td>1.72 (0.86 to 3.54)</td>
</tr>
<tr>
<td></td>
<td>75 mL</td>
<td>37 (38.1%)</td>
<td>15 (25.0%)</td>
<td>1.86 (0.92 to 3.92)</td>
</tr>
<tr>
<td></td>
<td>100 mL</td>
<td>35 (36.1%)</td>
<td>15 (25.0%)</td>
<td>1.70 (0.83 to 3.58)</td>
</tr>
<tr>
<td>Study 303</td>
<td>N = 209</td>
<td>N = 214</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 mL</td>
<td>84 (40.6%)</td>
<td>72 (33.6%)</td>
<td>1.35 (0.91 to 2.01)</td>
</tr>
<tr>
<td></td>
<td>75 mL</td>
<td>76 (36.7%)</td>
<td>62 (29.0%)</td>
<td>1.43 (0.95 to 2.15)</td>
</tr>
<tr>
<td></td>
<td>100 mL</td>
<td>72 (34.8%)</td>
<td>51 (23.8%)</td>
<td>1.71 (1.12 to 2.63)</td>
</tr>
</tbody>
</table>
## Exacerbations: Regional, By study, safety

<table>
<thead>
<tr>
<th>CF Exacerbations</th>
<th>Study 303</th>
<th>Study 302</th>
<th>Studies 301, 302, 303 Pooled adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM (N=56)</td>
<td>Control (N=59)</td>
<td>DPM (N=153)</td>
</tr>
<tr>
<td>SAEs</td>
<td>11 (19.6)</td>
<td>5 (8.5)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>AEs leading to drug discontinuation</td>
<td>6 (10.7)</td>
<td>3 (5.1)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>AEs leading to study withdrawal</td>
<td>4 (7.1)</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>3 (5.4)</td>
<td>2 (3.4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Any exacerbation</td>
<td>22 (39.3)</td>
<td>20 (33.9)</td>
<td>34 (22.5)</td>
</tr>
</tbody>
</table>