Regulatory perspectives on missing data in longitudinal analyses – a recent case study
Background: Cystic Fibrosis

Cystic fibrosis is a progressive, life threatening, genetic disease.

Multiple organ systems are involved but 90% of patients have respiratory involvement.

Because of the defect in the CFTR, airway liquid hyperabsorption causes impaired MCC, which is an important defense mechanism to maintain normal lung hygiene.

Impaired MCC causes mucus plugging and chronic airway obstruction, increasing the risk for pulmonary infection, inflammation and permanent loss of lung function.
Background: Cystic Fibrosis
Background: dry powdered mannitol (DPM)

Functions as an inhaled osmotic agent designed to improve and possibly correct the impaired MCC that is characteristic of CF and Bronchiectasis.

Bronchitol consists of 40 mg of spray dried mannitol powder encapsulated in size 3 hard gelatin capsules with no excipients and a dry powder inhaler.

A unique spray drying process produces primary particle size distributions in the desired range for delivery to the lung (mean aerodynamic particle diameters ~3μm)
Background: CF301 and CF302 trials

2x pivotal phase III trials

Primary efficacy endpoint = FEV$_1$
Primary efficacy variable = mean change from baseline over Weeks 6-26
Background: CF301 and CF302 trials

The FDA agreed that FEV1 was an acceptable primary endpoint provided that other supporting clinical endpoints were included in each study...

*FDA: Pulmonary function is monitored very closely in patients with cystic fibrosis, and progressively declines over the lifetime, at a rate as high as 1-4% of total function per year, so improvement in FEV1 would be considered clinically meaningful. In addition, cystic fibrosis lung disease as measured by FEV1 is correlated not only with pulmonary outcomes, but with longer term overall morbidity and mortality. The majority of death in the CF population is due to pulmonary causes, so improvement in FEV1 is a useful and clinically meaningful endpoint.*
Background: FDA

- Communications with the Pulmonary, Allergy, and Rheumatology division of the agency
- Different divisions within the FDA have different philosophies, opinions and preferences.
Background: Missing data in CF studies

<table>
<thead>
<tr>
<th>Disposition Category</th>
<th>Study 301</th>
<th>Study 302</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPM n (%)</td>
<td>Control n (%)</td>
<td>DPM n (%)</td>
</tr>
<tr>
<td>Intent-to-Treat Population</td>
<td>177 (63)</td>
<td>118 (41)</td>
<td>184 (63)</td>
</tr>
<tr>
<td>Week 26 Completers</td>
<td>112 (37)</td>
<td>86 (27)</td>
<td>153 (83)</td>
</tr>
<tr>
<td>Did not complete to Wk 26</td>
<td>65 (37)</td>
<td>32 (27)</td>
<td>31 (17)</td>
</tr>
<tr>
<td>Reasons:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>29 (45)</td>
<td>10 (33)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Withdrew Consent</td>
<td>28 (43)</td>
<td>22 (67)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Sponsor/MD decision</td>
<td>7 (11)</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Other c</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

FDA: In addition, early discontinuation from the double blind period continued to occur after week 6 resulting in missing FEV1 values for these patients at weeks 14 and/or 26. These discontinuations were more frequent in the DPM group in both studies.
The overriding statistical concern in the analyses of the efficacy data in studies CF301 and CF302 is the treatment-related frequent early dropouts. Analyses of the primary efficacy endpoint in a continuous form, as was intended in the protocol and SAP for each study are problematic in that they do not incorporate the entire ITT group.

The pre-specified primary statistical analysis method, mixed model for repeated measures (MMRM), requires an assumption that missing data occurred at random, unrelated to treatment. Since this assumption is violated in these studies...
Advisory committee (ad-com)

- Trial data
- Sponsor
- Presentations
- Pulmonary advisory committee (PADAC)
- Vote and recommendations
- FDA
In this application .... the most significant is the treatment-related early discontinuations that occurred disproportionally more often in the DPM-treated groups than the control groups.

...because the above analyses do not account for the frequent and treatment-related early discontinuations in the Phase 3 studies, the Agency does not feel the Applicant’s pre-specified primary efficacy analyses are an accurate reflection of the efficacy of DPM...
Six examples of treatment related study discontinuation:
(100 mL considered a clinically important improvement)

1. Experienced sore throat when taking drug...
2. Preferred hypertonic saline...
3. Withdrew as Tx was making his chest tight...
4. Too much effort and time in the mornings...
5. Stated he was 'not getting on' with the medication...
6. Causing excessive coughing, leaving him feeling exhausted...
Multiple imputation:
Two examples of late study discontinuation

50 imputations (PROC MI)

FDA
Multiple imputation:
Two examples of early study discontinuation

50 imputations (PROC MI)
Pattern mixture model: Multiple imputation + Penalty

Example:
Tipping point analysis

Logical extension of Pattern mixture model – how big must the penalty be before the results are no longer statistically significant?
Tipping point analysis: ANCOVA
Tipping point analysis: MMRM
T-test at Week 26

Tx: Completers
\( \mu = +124 \text{ mL} \)
\( \sigma = 232 \text{ mL} \)

Tx: All patients BOCF
\( \mu = +81 \text{ mL} \)
\( \sigma = 197 \text{ mL} \)
Tx: Completers
\[ \mu = +89 \text{ mL} \]
\[ \sigma = 307 \text{ mL} \]

Tx: All patients BOCF
\[ \mu = +76 \text{ mL} \]
\[ \sigma = 285 \text{ mL} \]
Tx: Completers
\[ \mu = +124 \text{ mL} \]
\[ \sigma = 232 \text{ mL} \]

Tx: All patients BOCF
\[ \mu = +81 \text{ mL} \]
\[ \sigma = 197 \text{ mL} \]

FDA #1 – perform t-test with point estimate from BOCF and \( \sigma \) from completers

FDA #2 – perform non-parametric test on BOCF data
FDA’s responder analysis

For this analysis, it was assumed that missing data at weeks 6, 14, or 26 represented a failure of DPM treatment. While a conservative approach, these data may be viewed as more representative of the entire CF population since those who could not tolerate treatment with DPM would not be expected to receive any benefit.
FDA’s responder analysis

FDA: With regard to the statistical significance of these findings, using the Van der Waerden test to determine the significance of the difference between treatment groups across a range of thresholds...

FDA: Because statistical hypothesis testing of the treatment effect over the entire range of thresholds, such as with the Van der Waerden test, is not standardized, generally accepted, straightforward statistical analyses were conducted to test for differences at different thresholds for efficacy...

Figure 1. Responder Analysis for Observed FEV1 Change from Baseline to Week 26

Study 301

Study 302
FDA’s responder analysis

*FDA: The Agency believes, from a statistical standpoint, that responder analyses that incorporate the entire ITT population and therefore account for the missing data from drop-outs, provide a more accurate reflection of the efficacy of DPM in the CF patients enrolled in the studies.*

*FDA: The nature of the most common reasons for early discontinuation suggest that these patients are experiencing an unsuccessful treatment in that if a patient cannot tolerate the product, no efficacy from the product should be expected.*
Pulmonary exacerbations

A multiple occurring event in CF, protocol specified analysis was negative binominal (or Poisson) model to estimate the rate ratio.

*FDA: In addition, the treatment-related early discontinuations previously described may have also impacted these results as patients who discontinued study participation early were not available to report the occurrence of these events.*
FDA: Since studies CF301 and CF302 differed in terms of the early discontinuation rate and pattern subgroup analyses are presented separately for each study...
Lessons, hindsight and ideas
Lessons, hindsight and ideas

Draw a sharp distinction between “treatment discontinuation” and “study discontinuation” in the protocol (banish the term “drop-out”). Make these clear to investigators and potential subjects.

Go to the ends of the Earth to get a Week 26 FEV\textsubscript{1} measurement.

Flexi-dosing?
Lessons, hindsight and ideas

Randomised withdrawal design
Commonly used in CF and accepted by the FDA
FDA: Sensitivity analyses... are problematic in that they attribute a good outcome to some patients who discontinue treatment or they impute a single score without accounting properly for variability.

FDA: Statistical procedures for appropriately handling missing data that cannot be avoided ... these methods should appropriately account for the variance in the treatment effect (i.e., multiple imputations) and should not be based on assumptions that perpetuate the treatment effect in the missing data.
Lessons, hindsight and ideas

BOCF
Lessons, hindsight and ideas

BOCF + noise

Repeat 50x

\[ \sim N(-10, 60) \quad \sim N(-20, 60) \]
Lessons, hindsight and ideas

BOCF + noise

50 imputations

μ = -10  μ = -20
EMEA: The Applicant could consider a strategy based on the Imputation Using Dropout Reason (IUDR) principle, where treatment related drop-outs (i.e. lack of efficacy, adverse events) are penalised. The latter method combined with multiple imputations to avoid shrinking of the variability appears to be a reasonable approach for the main analysis; however, other approaches than the complete case technique under the MCAR assumption may me considered acceptable whenever they are properly justified, and following all the requirements given in "CPMP/EWP/1776/99 Revl. Guideline on Missing Data in confirmatory trials".