In-Vitro /In-Vivo Comparisons of Formoterol MDI to Formoterol DPI: Lessons Learned

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Pearl FF MDI (PT005)

Considerations for initial dose selection

• In USA, no MDI approved at the start of development (either alone or in combination)
• Only Foradil Aerolizer (FA) available as a reference product
  - FA label is 12 mcg/capsule, which delivers 10mcg formoterol fumarate dihydrate (FFDH)
  - Pearl delivered dose is 9.6µg of FF anhydrous (per dose comprised of 2 actuations), equivalent to 10µg FFDH
• Overall NGI profile of MDI vs DPI known to be different when tested at the same flow rates. ¹
• Dilemma: Design studies to match on fine particle dose (FPD) vs total delivered dose (DD)?

In Vitro Comparisons
Representative Pearl MDI vs Foradil Aerolizer

Differences in flow rate dependence of devices make selecting clinical doses based on in vitro comparisons difficult and potentially misleading.

* Delivered dose determined using total impactor mass from aerodynamic particle size distribution measurement.
Decision Taken to Match Highest Emitted Dose

- Both products deliver approximately 10 µg formoterol fumarate dihydrate, (FFDH).
- Decision taken to match on DD
- If the FPD impacted either PK or lung function, could be assessed in clinic
- Initial study was a randomized, double-blind, single ascending dose design that included open label FA12 µg; the study had clearly defined patient withdrawal criteria.
PT0050801: Comparable Efficacy and Systemic Exposure at Same Nominal Dose (10µg FFDH)
PT0050801: Non-inferiority Assessment vs Foradil®

Data Support Non-inferiority for 9.6 µg Dose (LL 95%CI = -45 ml)
PT0050801: FF MDI 9.6 µg Comparable to FA12 (same nominal dose)

- **Efficacy:**
  - FF MDI 9.6 µg non inferior to FA 12 µg (lower bound 95% CI = -45 ml)

- **PK:**
  - Ratio of geometric LS Means for $C_{\text{max}}$ and $AUC_{0-12}$ within 100% ± 4%
  - Bioequivalence met for $AUC_{0-12}$

<table>
<thead>
<tr>
<th></th>
<th>$AUC_{0-12}$ Ratio of Geometric LS Mean (90% CI)</th>
<th>$C_{\text{max}}$ Ratio of Geometric LS Mean (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT0050801</td>
<td>96.8% (81.5, 114.96)</td>
<td>98% (79.59, 120.91)</td>
</tr>
</tbody>
</table>
PT0031002: FF MDI 9.6 µg Comparable to FA 12 µg

Mean Change in FEV₁ Over Time on Day 7 by Treatment vs Test Day Baseline (MITT Population)

- **FF MDI 9.6 µg**
- **Foradil 12 µg**
- **Placebo MDI**
PT0031002: FF MDI 9.6 µg Non-inferior to Foradil Aerolizer 12 µg at Steady State (Day 7)

Difference between FF MDI 9.6 µg and Foradil Aerolizer 12 µg was -0.016L (95% CI: -0.054, 0.022 L)
Study PT0031002: FF MDI 9.6 µg Bioequivalent to Foradil Aerolizer 12 µg at Steady State

FF MDI 9.6 µg vs Foradil Aerolizer 12 µg Pharmacokinetics
Ratio of Geometric LS Means (90% confidence intervals)

Bioequivalence target
PT005003 - Assay Sensitivity Demonstrated within Formulation Change from Baseline in FEV₁ AUC₀₋₁₂

- Assay sensitivity demonstrated within Foradil Aerolizer (Foradil) formulation
  - Foradil 24 µg is superior to Foradil 12 µg for FEV₁ AUC₀₋₁₂ (Difference = 52 mL; p-value = 0.002)
- Assay sensitivity demonstrated within FF MDI formulation:
  - FF MDI 19.2 µg superior to FF 9.6 µg for FEV₁ AUC₀₋₁₂ (Difference of 42 mL; p-value = 0.013)
PT005003: FF MDI 9.6 µg and FA 12 µg
Clinical Comparability and Bioequivalence

<table>
<thead>
<tr>
<th></th>
<th>AUC_{0-12} Ratio of Geometric LS Mean (90% CI)</th>
<th>C_{max} Ratio of Geometric LS Mean (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF MDI 9.6 µg vs Foradil 12 µg</td>
<td>96 (87, 105)</td>
<td>96 (87, 107)</td>
</tr>
</tbody>
</table>
PT003003: Cardiovascular Safety Study

Comparative 24-hour mean heart rate with FF MDI 9.6 µg and FA12 µg administration

- The bars represent the most extreme data points still within the 1.5 times above and below the inter-quartile range. The diamond represents the mean with the horizontal line within the interquartile range indicating the median.
- Individual extreme data points represent values more than 1.5 times above or below the inter-quartile range (the distance between the 25th and 75th percentile shown as the shaded areas)
## Summary: FF MDI 9.6 μg Compared with Foradil Aerolizer 12 μg

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Non-inferiority</th>
<th>Assay sensitivity</th>
<th>BE</th>
<th>Safety</th>
<th>24-hour Holter</th>
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</thead>
<tbody>
<tr>
<td>PT0050801</td>
<td>Single dose</td>
<td>√</td>
<td>√ §</td>
<td>§§</td>
<td>√</td>
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<tr>
<td>PT0031002</td>
<td>Chronic dose</td>
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<td>n/a</td>
<td>√</td>
<td>√</td>
<td>n/a</td>
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<tr>
<td>PT005003</td>
<td>Single dose</td>
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<td>√</td>
<td>n/a</td>
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<td>PT003003</td>
<td>Chronic dose</td>
<td>n/a</td>
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</tbody>
</table>

§ Assay sensitivity demonstrated within FF MDI formulation, 1 dose of FA evaluated.

§§ Study not powered for BE, comparability established with point estimates within 100 ± 4% for $C_{max}$ and $AUC_{0-12}$.
Conclusion

• FA 12 µg and FF MDI 9.6 µg deliver similar delivered dose (~10 µg of formoterol fumarate dihydrate).
• Differences were observed in FPD with clear flow rate dependence for FA 12 µg
• FA 12 µg and FF MDI 9.6 µg had equivalent PK, PD and comparable safety profile.
• Based on these results, both FPD and DD should be evaluated and considered when comparing test to reference, especially when delivery devices differ.