Case Study: Pharmacokinetics and Pharmacodynamics of Tiotropium and Salmeterol Following Parallel Administration in COPD Patients Using Different Dry Powder Inhalation Systems

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Introduction

Part of BI development program examining LABA/LAMA combinations
3 DPI administration modes:

- **Spiriva®HandiHaler®** (Tiotropium bromide)
- **Serevent®Diskus®** (Salmeterol Xinafoate)
- new T+S combination formulation with modified HandiHaler®

Overview of studies:
- In vitro characterizations, emphasizing APSD using ACI
- Pharmacokinetics in 47 COPD subjects
- Pharmacodynamics in same subjects
- Safety including ECG
The Active Ingredients

**Tiotropium Bromide**
Solubility: 25 mg/mL
Log P: -2.2
[BCS]: High solubility/low permeability
Renal excretion of unchanged material is main elimination pathway

**Salmeterol Xinafoate**
Solubility: ~ 60 µg/mL
Log P: 4.2
[BCS]: Low solubility/high permeability
Hydroxylation is main metabolic route followed by excretion in urine and feces
The Reference Products

High Resistance: 39 L/min for 4 kPa
Gelatin capsule
Lactose Carrier
5.5 mg powder fill
18 µg contained dose Tiotropium
~10 µg Delivered dose
~ 3.6 µg Impactor Sized Mass (S1-F)

Low Resistance: 60 L/min for 4 kPa
Unit blister
Lactose Carrier
12.5 mg powder fill
50 µg contained dose Salmeterol
47 µg Delivered dose
10.6 µg Impactor Sized Mass (S1-F)
Test Product T+S Combination with HandiHaler 2

Development goal: combination formulation of tiotropium bromide and salmeterol xinafoate matching respective ACI Impactor Sized Mass and stage distribution patterns of reference products (in vitro BE)

HandiHaler 2.0

HandiHaler 2.6
Ergonomics Exploratory

Same internal design concept/working principle as original HandiHaler
High Resistance: 39 L/min for 4 kPa pressure drop
Polyethylene capsule instead of gelatin
Lactose carrier but optimized selection with respect to lower and more uniform adhesion/cohesion characteristics
Clinical Trial Protocol Overview

- Randomised, open-label, 4-way crossover study with 4-week treatment periods
- 47 COPD patients

<table>
<thead>
<tr>
<th>DPI</th>
<th>Dosing</th>
<th>Tiotropium</th>
<th>Salmeterol</th>
</tr>
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<tbody>
<tr>
<td>Spiriva</td>
<td>QD</td>
<td>18 µg</td>
<td>---</td>
</tr>
<tr>
<td>Serevent</td>
<td>BID</td>
<td>---</td>
<td>50 µg</td>
</tr>
<tr>
<td>Spiriva + Serevent (Mono Combination)</td>
<td>QD, BID</td>
<td>18 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td>T+S HandiHaler 2.0</td>
<td>QD</td>
<td>7.5 µg</td>
<td>25 µg</td>
</tr>
</tbody>
</table>

- PD: 8 hour FEV₁ and FVC at steady state (covering trough and peak)
- PK: 8 hr profile at steady state
  - Tiotropium (plasma & urine); salmeterol (plasma)
  - Blood sampling: -5, 2, 5, 7, 10, 15, 20, 40, 50, 60, 70 min., 2, 4, 6 and 8 hr
  - No charcoal block
- Safety: 12-lead ECG, BP, AE, lab chemistry battery, physical exam
### T+S HandiHaler 2 Development Results

**Tiotropium**

#### Inhalable objectives met

- Significant reductions in unemitted & large particle fractions

<table>
<thead>
<tr>
<th>Device</th>
<th>Spiral HandiHaler</th>
<th>T+S HandiHaler 2</th>
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<tbody>
<tr>
<td>Contained Dose (µg)</td>
<td>18</td>
<td>7.5</td>
</tr>
<tr>
<td>Delivered Dose (µg)</td>
<td>10.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Impactor Sized Mass (µg)</td>
<td>3.6</td>
<td>3.5</td>
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Pharmacokinetics
Plasma Tiotropium

- Very rapid appearance of tiotropium in systemic circulation
- Co-administration of salmeterol does not influence tiotropium absorption or elimination
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<th>T+S HH2 : Reference (%)</th>
<th>Point Estimate (90% CI)</th>
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<tr>
<td>Reference</td>
<td>AUC $0-8$, ss (pg*h/mL)</td>
<td>$C_{\text{max}}$, ss (pg/mL)</td>
</tr>
<tr>
<td>Spiriva</td>
<td>111.8</td>
<td>147.1 (128.8 – 167.8)</td>
</tr>
<tr>
<td>(101.6 – 123.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiriva + Serevent</td>
<td>117.6</td>
<td>140.5 (123.2 – 160.3)</td>
</tr>
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<td>(107.3 – 129.0)</td>
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Pharmacokinetics
Urine Tiotropium

- Adjunct analysis in urine helps to verify plasma AUC results.
Pharmacokinetics
Urine Tiotropium

- Adjunct analysis in urine helps to verify plasma AUC results.
**T+S HandiHaler 2 Development Results**

**Salmeterol**

Significant reductions in unemitted & large particle fractions.

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<th>Contained Dose (µg)</th>
<th>Serevent</th>
<th>T+S HandiHaler 2</th>
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<tr>
<td>50</td>
<td>25</td>
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<th>Delivered Dose (µg)</th>
<th>Serevent</th>
<th>T+S HandiHaler 2</th>
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<td>47</td>
<td>21</td>
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<tr>
<th>Impactor Sized Mass (µg)</th>
<th>Serevent</th>
<th>T+S HandiHaler 2</th>
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<tr>
<td>11.6</td>
<td>11.4</td>
<td></td>
</tr>
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</table>
**Salmeterol APSD**

**Flow Rate Comparisons**

**Serevent @ 39 vs 70 L/min**
Delivery, Throat, Preseparator, ISM comparable
Shifts in Stage distribution pattern: cut-off diameter change + increased dispersal energy

**Serevent vs T+S HH2 @ 39 L/min**
ISM equivalent
“Non-inhalable” fraction ~4x greater for Serevent
Somewhat “finer” APSD for T+S HH2 but FPD within 15%
Pharmacokinetics
Plasma Salmeterol

- Very rapid appearance of salmeterol in systemic circulation
- Co-administration of tiotropium does not influence salmeterol absorption or elimination
- Very different profiles for HandiHaler 2 vs Serevent; secondary absorption component much less with HandiHaler 2
**Pharmacokinetics**

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<td>AUC (_{0-8,\ ss}) (pg*h/mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C(_{\text{max, ss}}) (pg/mL)</td>
</tr>
<tr>
<td>Serevent</td>
<td>59.6 (52.9 – 67.1)</td>
</tr>
<tr>
<td></td>
<td>133.0 (114.8 – 154.2)</td>
</tr>
<tr>
<td>Spiriva + Serevent</td>
<td>57.7 (51.3 – 64.9)</td>
</tr>
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<td></td>
<td>124.2 (107.3 – 143.7)</td>
</tr>
</tbody>
</table>
• Once-daily T+S HandiHaler 2 provided significantly more bronchodilation in terms of FEV$_1$ AUC$_{0-8h}$, and FEV$_1$ trough & peak compared to single-agent therapy as once-daily Spiriva or twice daily Serevent.

• No statistically significant differences were found between QD T+S HandiHaler 2 and the mono product combination of Spiriva (QD) plus Serevent (BID)
Pharmacodynamic Comparison
FVC

- FVC AUC\textsubscript{0-8h} and peak FVC: Results parallel those for FEV\textsubscript{1}.
- Trough FVC: T+S HandiHaler 2 vs Serevent alone was significant; T+S HandiHaler 2 vs Spiriva alone was not significant.
- No relevant and statistically significant differences were found between QD T+S HandiHaler 2 vs mono product combination of Spiriva plus Serevent
Safety Observations
QTcF was a systemic exposure discriminator

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time @ Maximum Difference</th>
<th>Difference* (ms)</th>
<th>Upper Bound 2-sided 90% CI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T+S HandiHaler 2</td>
<td>10 min</td>
<td>4.30</td>
<td>7.49</td>
</tr>
<tr>
<td>Serevent</td>
<td>40 min</td>
<td>3.92</td>
<td>7.13</td>
</tr>
<tr>
<td>Serevent + Spiriva</td>
<td>60 min</td>
<td>2.49</td>
<td>5.70</td>
</tr>
</tbody>
</table>

* Baseline reference was tiotropium mono treatment since no placebo arm included.

• QTcF changes mirror PK $T_{\text{max}}$
Findings & Conclusions (1)  
In the Context of Ongoing BE and IVIVC Debates

For tiotropium:
- ISM correctly anticipated AUC equivalence for the two HandiHaler configurations.
- APSD qualitatively anticipated differences in plasma $C_{\text{max}}$ but missed on magnitude of difference.
- Simultaneous urine sampling adds power to BE estimates from plasma AUC.

For salmeterol:
- Greater mass deposition in throat and preseparator corresponds to greater secondary absorption from Serevent Diskus.
- Because no charcoal block was included in the study, it was not possible to determine if the secondary absorption occurred orally, was due to prolonged dissolution-limited lung absorption, or a combination of both effects.
- Major differences in observed $C_{\text{max}}$ were not expected based on ACI Stage deposition patterns.
Findings & Conclusions (2) 
In the Context of Ongoing BE and IVIVC Debates

- In vitro results were not predictive for PK
- PK is highly discriminating for safety inferences.
- Lung function PD when dosing in “plateau” region is once again shown to be a poorly discriminating BE metric.
- Acceptance of systemic PK as a reliable surrogate for LAMA or LABA airway pharmacologic effect is still lacking scientific validation.
- Parallel PK and PD at steady state in patients is a manageable protocol that avoids separate studies and eliminates questions about the relevance of using normal subjects (the patient interface dilemma).
- PK studies should include administration with and without an oral absorption inhibitor for any low solubility API with meaningful secondary oral absorption potential.
• Matching in vitro APSD as the sole test of DPI bioequivalence is beyond the capability of current pharmacopoeial test platforms.
• Advances toward IVIVC have been made using more biorelevant in vitro platforms and test conditions, i.e., breath simulators, anatomic models.
  - Such systems are now commercially available.
  - Representative inhalation profiles for COPD and asthma patients are also accessible.
  - Published data to better understand & validate IVIVC’s with these models is needed
  - Any publication or regulatory submission that does not include data from a biorelevant in vitro system should no longer be considered as “state of the art”.
• If there is a parallel to a Biopharmaceutics Classification System for pulmonary absorption, the permeability component seems to be much less important compared to oral BCS.