Phase 0 Microdosing Studies with Renin Inhibitors

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Overview of Today’s Presentation

- Background of Speedel and Renin Inhibitors
- Speedel’s issues in choosing Microdosing
- Technical issues in using Microdosing
- Example of Microdosing using Renin Inhibitors
- Benefits of Microdosing from Speedel’s perspective
Background

- These studies were performed in 2004 before the CREAM Trial was published
- Speedel was a biopharmaceutical company with 61 employees with extensive use of external contractors
- Speedel’s first compound Aliskiren (Tekturna®/Rasilez®) was in Phase III development with Novartis
- There were several possible follow-up candidates to Aliskiren
- Speedel was bought by and integrated into Novartis in 2008

The Renin-Angiotensin System

Renin Specificity and Inhibition by Aliskiren

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>IC_{50} (nM)</th>
<th>Species (Renin)</th>
<th>IC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>0.07</td>
<td>Human</td>
<td>0.6</td>
</tr>
<tr>
<td>Cathepsin D</td>
<td>500</td>
<td>Marmoset</td>
<td>2</td>
</tr>
<tr>
<td>Cathepsin E</td>
<td>&gt;10,000</td>
<td>Dog</td>
<td>7</td>
</tr>
<tr>
<td>HIV-1 protease</td>
<td>&gt;10,000</td>
<td>Rabbit</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guinea pig</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rat</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fish</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cat</td>
<td>&gt;5000</td>
</tr>
</tbody>
</table>

Adapted from Jensen et al. Nature Reviews Drug Discovery 2008
**Renin Inhibitors – PK/PD Relationship**

![Graph](image-url)

Adapted from Nussberger et al. Hypertension 2002

**Increasing Bioavailability Improves Dose-Response On Blood Pressure in Double Transgenic Rats**

![Graph](image-url)

Source: Speedel – R&D Day 2006

**Pros and Cons of Use of Microdosing**

**Microdosing should allow an early selection of potential clinical candidates based on human pharmacokinetic data**

Pros: Absorption, Distribution, (Metabolism) and Elimination can be studied in Man (PK)
Cons: Does not reveal direct information on efficacy (PD)

**Development time**

Pros: Microdosing: From lab to man in < 9 months without expensive drug manufacturing and toxicology testing for Phase I
Cons: Tolerability and surrogate measures of efficacy cannot be assessed without adding another layer of development

Toxicology results for microdosing cannot be used for safety assessment for a classical Rising-Dose-Tolerability Study

**Applicability of Results**

The studies were performed prior to the completion of the CREAM Trial
**Microdosing Partners**

<table>
<thead>
<tr>
<th>Clinical Trial and Drug Formulations</th>
<th>Sponsor</th>
<th>Analytics (AMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharma Bio-Research Groningen, NL (PRA International)</td>
<td>Speedel Pharma, Basel, CH (Novartis AG, Basel, CH)</td>
<td>Xceleron Ltd., York, UK</td>
</tr>
</tbody>
</table>

**Study Design for Bioavailability**

- **Dose and Administration**
  - 6 Healthy Male Volunteers
  - Cross-over administration of Test Compound
  - 100 μg Test Compound containing 100 nCi 14C-RI
    - Oral Dose in Solution
    - Intravenous dose via 10 minute infusion
- **Analytics**
  - Concentration of « Total » 14C (Parent + metabolites)
  - Separation of Parent Drug from metabolites by HPLC for determination of « Parent » Drug

**Toxicology Program**

**Mutagenicity Testing**

**Ames and Chromosomal Aberration**

**In-life**

**Dogs**
- 2 mg/kg single dose, oral and intravenous
- Males and female animals
- EKG and clinical observation

**Rats**
- 2 mg/kg single dose, oral and intravenous
- Males and females
- Clinical observation and necropsy
Technical Issues Encountered

- Radioactive Synthesis
  - GMP Requirements
  - Major Difference in Synthesis of “hot” versus “cold” material
- Drug Formulation at Low Doses
  - Very dilute concentrations of drug (25 g/ml)
  - Drug absorption to containers and tubing
  - CRO selection - ability to work with radioactive formulations
- “Pooled” Sampling vs Individual Sampling
  - High cost per sample
  - Inter-subject variation
- Method Development for HPLC Extraction of Parent Drug and Metabolites
  - Long elution times up to 70 minutes per sample
  - Unknown profiles of possible metabolites

Sample Analysis – Pooling versus Individual Samples

- Two-step Approach
  - Pooled Samples
    - Total 14C measurement
    - HPLC for Parent Drug
  - Individual Measurements
    - Total 14C measurement
    - HPLC for Parent Drug
- Cost Considerations
  - Pooling – 8 samples
  - Individual – 240 samples
HPLC Separation of Parent Drug and Metabolites

Determination of Parent Drug and Metabolites

Microdosing – Individual Variation following Intravenous Dosing of SPP601
Microdosing of SPP601 – Urinary Excretion of $^{14}$C

Mean Urine Excretion

Cumulative % dose vs. Time (h)

IV dose vs. Oral dose

Plasma Levels of SPP601, SPP630, and SPP635 Following Single Oral and IV Microdoses (100 g) in Male Subjects

SPP635: Plasma Concentration-Time Curves in Man Following Single Oral Doses

Relative Plasma Concentration vs. Hours

SPP635 Single Dose at Therapeutic Level vs. SPP635 Microdosing

Source: Speedel R&D Day 2006
Benefits to Speedel in Using Microdosing

- Enabled the selection of the best of three candidates for further clinical development in a short period of time
- Gained valuable information in man for the future development of Renin inhibitors
- Decreased the amount of time and resources required for drug manufacturing and toxicology testing by 1/3
- Decreased risk of selecting the wrong candidate while increasing the chance of selecting the right candidate for clinical research

Contact

Thank you for your attention

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