Case Example: Exposure Response to Support Extrapolation of Efficacy in Pediatric Ulcerative Colitis

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Remicade® (infliximab)

A chimeric (human/murine) IgG 1 monoclonal antibody specific for human tumor necrosis factor α (TNFα)

• Neutralizes biological TNFα activity by binding to TNFα and inhibiting its ability to bind to receptors

Approved Indications

• Dermatology: Plaque Psoriasis
• Rheumatology: Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis
• Gastroenterology: Adult Crohn’s disease, Adult Ulcerative Colitis, Pediatric Crohn’s disease, Pediatric Ulcerative Colitis (≥ 6 y.o.)
General Approach to Extrapolation of Efficacy in Pediatric UC

The **course of the disease** and **response to treatment** are expected to be sufficiently similar between adults and children with UC.

It was not clear whether a similar exposure-response relationship in children and adults could be assumed.

Explored support for partial extrapolation of efficacy through PK & exposure-response analyses.
Pediatric UC (T72) Study

**INDUCTION PHASE**

- Open-label Single arm
- 5 mg/kg IV at **Weeks 0, 2, 6** (N=60)

**Week 8**

- Responders Randomized 1:1

**MAINTENANCE PHASE**

- **Q8W Group:** Open-label 5 mg/kg IV every 8 weeks
  - **Weeks 14, 22, 30, 38, 46** (N=22)

- **Q12W Group:** Open-label 5 mg/kg IV every 12 weeks
  - **Weeks 18, 30, 42** (N=23)

- Open label
- Single arm induction phase with no control/comparison group
- Small sample size

*FDA slide presented at Advisory Committee Meeting dated 7/21/11*
Pediatric Dose Selection

• In T72, the dose selected for study was based on data from adult and pediatric CD and adult UC studies/approved doses and indications:
  
  – Adult IBD doses
    • Crohn’s Disease: IND: 5mg/kg IV 0, 2, 6 weeks; MAINT: 5mg/kg IV q8 weeks, *(may ↑ to 10mg/kg)*
    • Ulcerative Colitis: IND: 5 mg/kg IV 0, 2, 6 weeks, MAINT: 5mg/kg IV q8 weeks

  – Pediatric IBD doses
    • Crohn’s Disease: IND: 5mg/kg IV 0, 2, 6 weeks; MAINT: 5mg/kg IV q8 weeks
    • Ulcerative Colitis: IND: 5 mg/kg 0, 2, 6 weeks; MAINT: 5mg IV q8 weeks

Adapted from FDA slide presented at Advisory Committee Meeting dated 7/21/11
Induction Phase: Week 8 Median Concentrations and Response Rates Similar Between Populations based on Primary Endpoint (Clinical Response)

<table>
<thead>
<tr>
<th></th>
<th>T72 Pediatric UC (5mg/kg)</th>
<th>ACT1 Adult UC (5mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Treated</td>
<td>60</td>
<td>121</td>
</tr>
<tr>
<td>Responder*</td>
<td>44</td>
<td>83</td>
</tr>
<tr>
<td>Response Rate</td>
<td><strong>73%</strong></td>
<td><strong>69%</strong></td>
</tr>
<tr>
<td>Median (90% CI) Concentration at Week 8 (µg/mL)</td>
<td><strong>29 (12 ~ 48)</strong></td>
<td><strong>33 (7 ~ 64)</strong></td>
</tr>
</tbody>
</table>

* A decrease from the baseline Mayo score of ≥ 30 percent and at least three points, with a decrease in the rectal bleeding subscore of at least 1 or a rectal bleeding subscore of 0 to 1.
Induction phase: Exposure-Response Relationships between Adults and Pediatric Patients Appear Similar based on Primary Endpoint

Induction Phase

FDA Slide adapted from Office of Clinical Pharmacology presented at Advisory Committee Meeting 7/21/2011
Maintenance Phase: Limited Data to Support Exposure Response Evaluation

• PK exposure response data limitations
  – Few pediatric patients with both PK and clinical response (N=9) or clinical remission data (N=17) at Week 54

• Leveraged clinical observations to support the maintenance dose
Clinical Observations that Supported the Maintenance Dose (1)

Patients in Clinical Remission at Week 54

<table>
<thead>
<tr>
<th></th>
<th>T72</th>
<th>ACT 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFX 5 mg/kg</td>
<td>IFX 5 mg/kg</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients randomized</td>
<td>22</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Patients with evaluable PUCAI (T72) or Mayo (ACT 1) at Week 54</td>
<td>21</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Patients in clinical remission at Week 54</td>
<td>8/21 (38%)</td>
<td>42/121 (35%)</td>
<td>20/121 (17%)</td>
</tr>
</tbody>
</table>

T72: Pediatric UC trial; ACT1: Adult UC trial

FDA slide presented at Advisory Committee Meeting dated 7/21/11
Clinical Observations that Supported the Maintenance Dose (2)

- Fewer pediatric patients required step-up therapy or discontinued treatment in the 5 mg/kg q8w group

<table>
<thead>
<tr>
<th>Dose Group (N)</th>
<th>Step-up</th>
<th>Discontinued*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg q8w (22)</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>5 mg/kg q12w (23)</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

* Includes patients who discontinued regardless of step-up
Conclusions

- Similar exposure-response relationships of response and remission between adults and pediatrics in the induction phase supported partial extrapolation of efficacy from adults that supported pediatric labeling for induction with Remicade.

- Demonstration of similar exposure-response relationships during induction phase, combined with clinical observations in the maintenance phase, supported dose selection in the maintenance phase.
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