Cosentyx in psoriasis

*We need(ed) both, exploratory and confirmatory*

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2nd EFSPi Workshop on Regulatory Statistics
Oct 06, 2017

→ for disclaimer, see last slide
 Confirmatory & exploratory

We Need Both Exploratory and Confirmatory
Author(s): John W. Tukey
Published by: American Statistical Association
Summary

• Development program relied on complementary approaches: exploratory pharmacometric analysis and confirmatory statistics

• Simulations based on pharmacometric model allowed to go into phase III with two dosing regimens that had not been tested previously

• Efficacy and safety (and model-based predictions) for these regimens were confirmed in phase III

• Secukinumab (Cosentyx) has since been approved for moderate to severe psoriasis in US, EU and many other countries
**Comprehensive development program**

Nine studies in ~4,000 psoriasis patients

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study*</th>
<th>Description</th>
<th>Secukinumab Dosing Regimen</th>
<th>Number of Psoriasis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph II</td>
<td>A2102</td>
<td>Proof of concept (i.v.)</td>
<td>1 x 3 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2220</td>
<td>Low dose-ranging (s.c.)</td>
<td>25, 75, or 150 mg</td>
<td>570</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1x or monthly)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2212</td>
<td>High dose ranging (i.v.)</td>
<td>3 or 10 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1x or 3x)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2211</td>
<td>Regimen finding: with/without loading (s.c.)</td>
<td>150 mg (1x, monthly, or “early”)</td>
<td></td>
</tr>
<tr>
<td>Ph III</td>
<td>A2302</td>
<td>Placebo controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2303</td>
<td>Placebo and etanercept controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2308</td>
<td>Prefilled syringe</td>
<td></td>
<td>3369</td>
</tr>
<tr>
<td></td>
<td>A2309</td>
<td>Autoinjector</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2304</td>
<td>Fixed vs. start-of-relapse</td>
<td></td>
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</tr>
</tbody>
</table>
Iterative modeling & predictions to choose phase 3 dosing regimens

- **iv POC study**
- **iv/sc bioavailability**

### iv high dose
- **PhIIb; N ≈ 100 ptn**
- **wk12 primary**
- **interim**
- 1) Build model & predict induction
- 2) Update model & predict maintenance
- 3) Include maintenance/relapse & predict next readout

### sc regimen
- **PhIIb; N ≈ 396 ptn**
- **wk12 primary**
- **interim**
- 3) Simulations for phase III regimen

### sc lower doses
- **PhIIb; N ≈ 120 ptn**
- **wk12 primary**
- 3) Simulations for phase III regimen
D-E-R relation described by pharmacometric PK/PD model

- Model describes dose-exposure-response relationship by compartments (using differential equations) and mixed effects (to characterize variability)
- Model validation by goodness-of-fit, visual predictive checks, and prospective prediction
Phase 2 data made modeling necessary and feasible

Program benefit from modeling

• Bridging across routes, doses, regimens, studies

• Primary endpoint (wk 12) not at steady-state & delay in response

• Optimizing onset, maximum response, maintenance

• Combinatorial optimization of complex regimens not feasible in studies

Modeling benefit from program

• Well-behaved endpoint

• Wide dynamic range of inputs and exposure

• Staggered studies allow iterative modeling building and qualification
Predictions suggested optimized performance for selected regimens
Various endpoints to be included in Phase 3 trials for competitive labeling

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-primary Endpoints</strong></td>
<td>Psoriasis Area and Severity Index (PASI) 75 response</td>
</tr>
<tr>
<td></td>
<td>Investigator Global Assessment: clear or almost clear skin</td>
</tr>
<tr>
<td><strong>Key Secondary Endpoints</strong></td>
<td>PASI 90 response</td>
</tr>
<tr>
<td></td>
<td>Psoriasis Patient Diary: itch, scaling, pain</td>
</tr>
<tr>
<td><strong>Important Secondary Endpoints</strong></td>
<td>PASI 100 response</td>
</tr>
<tr>
<td></td>
<td>Dermatology Life Quality Index (DLQI)</td>
</tr>
</tbody>
</table>
Endpoints ordered by clinical importance in Phase 3 testing strategy

150 mg

$H_1 v H_3$

$H_5$

$H_7$

$H_9$

$H_{11}$

$H_2 v H_4$

$H_6$

$H_8$

$H_{10}$

$H_{12}$

$\alpha/2$

$\alpha/2$

150 mg

300 mg

PASI 75 and IGA 0 or 1 response at Week 12 superiority versus placebo

PASI 90 response at Week 12 superiority versus placebo

Psoriasis Diary item pain at Week 12 superiority versus placebo

Psoriasis Diary item itch at Week 12 superiority versus placebo

Psoriasis Diary item scaling at Week 12 superiority versus placebo
Confirmation of predictions

Predictions of Efficacy for Phase III
Based on the Phase II data set

Pooled Phase III Data
PASI 75 at Week 12
Response Rate (%)

- 300 mg: 79.4%
- 150 mg: 69.2%
- 75 mg

Dosing:

Time (weeks)

Predicted PASI 75 Response Rate (%)
Further applications of PKPD modelling: exposure-AE, PoS calculations

- Exposure-AE

- Probability of success

Nasopharyngitis (PT), 300mg group
Collaboration

How to make it work

• Learn
• Share information / include
• Be open-minded
• Respect
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Aspiring to become more versatile, quantitative drug developers
Thank you
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