Extrapolation in paediatric juvenile idiopathic arthritis: case study

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Extrapolation in juvenile idiopathic arthritis (JIA)

Certolizumab pegol (CZP) case-study

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Certolizumab pegol

- A humanized antibody antigen-binding fragment (Fab’) with high specificity for human TNFα
- Linear PK, elimination T_{1/2} of 14 days
- Administered via subcutaneous injection

- Approved in Europe for treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (AxSpa) including ankylosing spondylitis (AS) in adults.
- Posology – 400 mg (week 0, 2, 4) followed by 200 mg every 2 weeks thereafter or an alternative 400mg every 4 weeks dose regimen can be considered

Juvenile idiopathic arthritis

Persistent arthritis of unknown aetiology with onset prior to 16 years of age

- Most commonly diagnosed paediatric rheumatic disease, prevalence ~100 in 100,000
- Symptoms of limping, stiffness, irritability, weight loss, delayed maturation etc.
- Depending on severity, treatment typically includes disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, and may progress to include biologic agents

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International League of Associations for Rheumatology (ILAR) JIA Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Systemic arthritis</td>
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<tr>
<td>Oligoarthritis, persistent</td>
<td></td>
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<tr>
<td>Oligoarthritis, extended</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis, rheumatoid factor +/-</td>
<td>&gt;4 joints/polyarticular-course</td>
</tr>
<tr>
<td>Psoriatic arthritis (PsA)</td>
<td></td>
</tr>
<tr>
<td>Enthesitis-related arthritis (ERA)</td>
<td></td>
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<tr>
<td>Undifferentiated</td>
<td></td>
</tr>
</tbody>
</table>

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1 Perry RE et al, J Rheumatol 2004; 31(2):390-2
CZP JIA clinical trial programs overview

- JIA study RA0043 ‘PASCAL’\(^1\) – enrollment completed, dosing ongoing
  - FDA postmarketing requirement
  - Open-label investigation of CZP PK, safety, and efficacy
    - Moderately to severely active polyarticular-course JIA, 2-17 years old
    - Inadequate response/intolerance to prior DMARDs
    - Enrollment in North America, South America, Russia

- JIA study JA0002 – planned
  - As described in agreed PIP (EMEA-001071-PIP02-12-M01)
  - Similar in design to RA0043

- **NOTE**: CZP is not indicated for use in pediatric patients

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\(^1\)ClinicalTrials.gov identifier: NCT01550003
Evidence to support efficacy extrapolation

In keeping with EMA guidance documents:
2012 extrapolation (129698) and 2015 JIA (239770)

- Children with polyarticular-course JIA are expected to respond to treatments comparably to adults with RA
- Adults and paediatric conditions represent inflammatory arthritis
- Efficacy studies can potentially be waived “in well-studied pharmacological classes”, or when considerable amount of data has been collected in adults (eg licensed indication in one or more of the corresponding adult arthritis categories)
- When the paediatric development plan was negotiated:
  - Two other TNF-antagonists (etancercept and adalimumab) were approved in US and EU for the treatment of both RA and JIA
    - Although no direct quantitative similarity between key efficacy scales (ACR and PedACR respectively)
  - CZP was approved for RA
Extrapolation of exposure

Data from two phase 3 studies and a population PK and PK-PD model\(^1\) were used for the extrapolation approach

- Recommended dosing regimen in adults with RA is 400 mg at weeks 0, 2 and 4 followed by 200 mg Q2W thereafter
- \(C_{avg50}\) = average concentration leading to 50% of the maximum ACR20 response was 16.8 ug/mL [95% CI:10.2 to 23.4]
- Assumed that the target therapeutic concentration required in paediatrics was similar to that in adults
- Applied allometric scaling to propose dose/regimen for children >2 years with BW >10 kg using the relationship:

\[
V_{ped} = V_{adult} \times (\frac{W_{ped}}{70})
\]

\[
CL_{ped} = CL_{adult} \times (\frac{W_{ped}}{70})^{0.75}
\]

\(^1\) Lacroix BD, \textit{et al.} \textit{Pharmacol Ther.} 2009 Oct;86(4):387-95
**Allometric scaling results**

Initial predictions suggested that a dose reduction in subjects <40 kg should achieve the target concentrations

<table>
<thead>
<tr>
<th></th>
<th>Loading dose (weeks 0, 2 and 4)</th>
<th>Treatment dose (week 6 onwards)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to &lt; 20 kg</td>
<td>100 mg (0, 2, 4)</td>
<td>50 mg Q2W</td>
</tr>
<tr>
<td>20 to &lt; 40 kg</td>
<td>200 mg (0, 2, 4)</td>
<td>100 mg Q2W</td>
</tr>
<tr>
<td>≥ 40 kg</td>
<td>400 mg (0, 2, 4)</td>
<td>200 mg Q2W</td>
</tr>
</tbody>
</table>

Trial simulations (TS) were performed in TS2, to evaluate:

- Adequacy of the proposed dosing regimen in terms of matching exposure measures (Cmax, Ctrough, and AUC)
- Expected incidence of anti-CZP-antibodies relative to adults
- Precision of CL/F and V/F depending on overall sample-size
Predicted steady-state (week 14-16) PK parameters

Stratified by age group

Box-and-whisker plots of $C_{\text{max}}$ by age group

Box-and-whisker plots of $\text{AUC}_{\tau}$ by age group

Expected precision of parameters based on a sample-size of 125 across the entire age/weight range was high, <10 % for CL/F and V/F
Predicted $C_{\text{trough}}$ and expected anti-drug antibody incidence

Table 9:3 Summary of $C_{\text{trough}}$ values and anti-body incidence

<table>
<thead>
<tr>
<th>Age Group</th>
<th>$C_{\text{trough}}$ (μg/mL)</th>
<th>Range</th>
<th>% &lt; 10 μg/mL (ratio)</th>
<th>% Anti-body Positive (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (ratio$^{(a)}$)</td>
<td></td>
<td>% Anti-body Positive (ratio$^{(a)}$)</td>
<td></td>
</tr>
<tr>
<td>4 - 8 yrs</td>
<td>13.4 (0.84)</td>
<td>0.011 - 67.5</td>
<td>31.1 (1.59)</td>
<td>7.7 (1.01)</td>
</tr>
<tr>
<td>5 - 12 yrs</td>
<td>15.4 (0.96)</td>
<td>0.265 - 76.1</td>
<td>22.3 (1.14)</td>
<td>6.1 (0.80)</td>
</tr>
<tr>
<td>13 - 17 yrs</td>
<td>18.5 (1.16)</td>
<td>0.426 - 65.8</td>
<td>14.8 (0.76)</td>
<td>6.7 (0.88)</td>
</tr>
<tr>
<td>Adult</td>
<td>16</td>
<td>0.234 - 59.8</td>
<td>19.5</td>
<td>7.6</td>
</tr>
</tbody>
</table>

$^{(a)}$ pediatric to adult ratio

Data on file
Planned model-based interim analysis

Conducted after 36 subjects had been enrolled

- Overall, the exposure appeared higher in paediatric subjects compared with adults
- during both the loading phase (weeks 0, 2 and 4),
- and during the maintenance phase (post-week 6)
- Population analysis performed, combining data from adult RA population in western countries and Japan and available data from RA0043
- Subsequent model was used to perform a series of simulations to evaluate a more optimal dosing algorithm
Simulations

Paediatric population with realistic WT-HT-AGE distribution was constructed based on demographic data from NHANES.

Paediatric subjects appear to have a lower CL/F and V/F compared to adults.
Overall predicted exposure ranges based on interim data

Higher exposures during loading and maintenance phase

Data on file
**Dose optimization**

Evaluate optimal dose and weight/BSA cut-off

<table>
<thead>
<tr>
<th>Weight range</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% of current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt; 20 kg</td>
<td>50 mg Q2W</td>
<td>50 mg Q4W</td>
</tr>
<tr>
<td>20 to &lt; 40 kg</td>
<td>100 mg Q2W</td>
<td>50 mg Q2W</td>
</tr>
<tr>
<td>≥ 40 kg</td>
<td>200 mg Q2W</td>
<td>100 mg Q2W</td>
</tr>
<tr>
<td>Optimized WT cut-off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt; 21 kg</td>
<td>50 mg Q2W</td>
<td>50 mg Q4W</td>
</tr>
<tr>
<td>21 to &lt; 41 kg</td>
<td>100 mg Q2W</td>
<td>50 mg Q2W</td>
</tr>
<tr>
<td>≥ 41 kg</td>
<td>200 mg Q2W</td>
<td>100 mg Q2W</td>
</tr>
<tr>
<td>Optimized BSA cut-off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.47 to &lt; 0.84 m²</td>
<td>50 mg Q2W</td>
<td>50 mg Q4W</td>
</tr>
<tr>
<td>0.84 to &lt; 1.21 m²</td>
<td>100 mg Q2W</td>
<td>50 mg Q2W</td>
</tr>
<tr>
<td>≥ 1.21 m²</td>
<td>200 mg Q2W</td>
<td>100 mg Q2W</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>400 mg Q2W</td>
<td>200 mg Q2W</td>
</tr>
</tbody>
</table>

1 The optimal dose estimated to be 25 mg Q2W, but the lowest available dose size is 50 mg. A 50 mg Q4W dosing regimen was used instead of 25 mg Q2W
Trial adaptation

All three evaluated dosing regimens could match the target Css average in adults, 50% of current dosing regimen appeared most pragmatic

This interim analysis resulted in a protocol amendment and a reduced dosing was implemented
Conclusions

Extrapolation allows program optimization

- No dose-finding study conducted in paediatric population
- No controlled efficacy clinical trial needed
- Open label design of pediatric study facilitated recruitment and reduced sample size in this vulnerable population
- Health authorities consultation and feedback:
  - Study design (RA0043) and use of extrapolation agreed by FDA
  - Similar study design (JA0002) and extrapolation plan included in the agreed PIP (EMEA-001071-PIP02-12-M01)