A COMPARISON OF PK AND PD OUTCOMES OF TOCILIZUMAB IN GIANT CELL ARTERITIS AFTER SC AND IV DOSING

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DISCLOSURES

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TCZ for the Treatment of Patients With GCA

• TCZ is a humanized anti–IL6-R monoclonal antibody indicated globally for the treatment of RA, GCA, pJIA, and sJIA and in the United States of CRS¹

• Evidence for TCZ approval in GCA came from a double-blind, phase III RCT (GiACTA)²
  – GCA patients received SC 162 mg TCZ either QW or Q2W

• A phase II RCT also showed positive outcomes³
  – GCA patients received TCZ IV 8 mg/kg Q4W

• The double-blind dosing portion of each study lasted ~1 year

CRS, cytokine release syndrome; GCA, giant cell arteritis; IL-6R, interleukin-6 receptor; IV, intravenous; pJIA, polyarticular juvenile idiopathic arthritis; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; RA, rheumatoid arthritis; RCT, randomized, controlled trial; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis; TCZ, tocilizumab.

Efficacy of TCZ Regimens in GCA

- All 3 treatment regimens resulted in positive outcomes for sustained remission of GCA
  - Both TCZ SC regimens in the GiACTA trial, were superior to placebo for the achievement of sustained remission\(^1\)
  - However, a higher benefit was noted in some key secondary efficacy outcomes with the SC QW vs the SC Q2W regimen\(^1\)
    - On average, patients on the QW regimen experienced longer time to first GCA flare than those on the Q2W regimen
  - TCZ IV also induced remission compared with placebo in the phase 2 trial\(^2\)

PK/PD Analysis: Objective and Methods

- **Objective**
  - To characterize the PK of TCZ in the GCA population and to assess the impact of the exposure differential from the 3 regimens (TCZ IV Q4W, TCZ SC QW, and TCZ SC Q2W) on PD markers

- **Methods**
  - TCZ levels and PD biomarkers (sIL-6R, IL-6, ESR, and CRP) were measured using validated assays at regular intervals throughout the dosing period from all patients in each trial
  - PK and PD outcomes were compared to facilitate understanding of the dose exposure–response relationships from IV and SC administration

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PD, pharmacodynamics; PK, pharmacokinetics; sIL-6R, soluble interleukin-6 receptor.
Comparison of concentration-time profile of TCZ after SC and IV dosing in GCA patients

Data are shown as mean, SD of TCZ serum concentrations, n = 98 for SC QW, n = 43 for SC Q2W and n = 14 for IV Q4W regimen
**Median Steady State Trough Exposure of TCZ at Week 52**

- $C_{\text{trough}}$ is a primary PK driver of TCZ efficacy
- IV exposures were within the range of exposures of the SC regimens

**Graph:**
- BL, baseline; $C_{\text{trough}}$, mean trough steady state exposure.
- Data are shown as medians, 25th to 75th percentiles (boxes), 2.5th to 97.5th percentiles (whiskers), and triangles denote outliers (GraphPad Prism 6.07).
PD: Median sIL-6R Levels at Week 52

- sIL-6R is a mechanistic marker reflecting target engagement of the IL-6 receptor by TCZ
- sIL-6R levels were similar for the IV Q4W and SC QW regimens but lower for the SC Q2W regimen
  - Suggests a higher level of target engagement from the IV Q4W and SC QW regimens vs the Q2W regimen
  - Exposures from the IV Q4W and SC QW regimens are expected to result in saturation of IL-6R during the dosing interval

Data are shown as medians, 25th to 75th percentiles (boxes), 2.5th to 97.5th percentiles (whiskers), and triangles denote outliers (GraphPad Prism 6.07).
• IL-6 levels increased vs baseline after TCZ administration for all 3 regimens
  – This reflects displacement of bound, endogenous IL-6 from its receptor, consistent with the mechanism of action of TCZ

Data are shown as medians, 25th to 75th percentiles (boxes), 2.5th to 97.5th percentiles (whiskers), and triangles denote outliers (GraphPad Prism 6.07).
ESR levels decreased to a similar extent in response to TCZ administration with all 3 regimens.
• Change from baseline in CRP was comparable between the SC regimens (~79% and 93% reductions from baseline from the QW and Q2W regimens, respectively)
• Quantitative changes in CRP values are not available for the IV study

Data are shown as medians, 25th to 75th percentiles (boxes), 2.5th to 97.5th percentiles (whiskers), and triangles denote outliers (GraphPad Prism 6.07).
Conclusions

• Comparison of $C_{\text{trough}}$ after 52 weeks of dosing with TCZ IV and TCZ SC showed that exposures for the IV regimen were within the range of exposures for the QW and Q2W regimens

• Comparison of PD outcomes showed that all 3 regimens had similar results, with the possible exception of lower levels of sIL-6R from the SC Q2W regimen
  – Lower sIL-6R levels observed with the SC Q2W regimen suggest lower target engagement, which may explain some of the efficacy differences compared with the SC QW regimen

• PK and PD results are consistent with the similar efficacy outcomes seen in the SC and IV trials
Back-up
TCZ-treated patients showed a mean flare-free survival time 25 weeks longer than placebo-treated patients (95% CI: 11, 39) (p=0.0005)
Time to First Flare Following Clinical Remission after SC dosing

Primary endpoint

Zone where 26 wk prednisone taper reaches 0 mg/day

Patients without GCA flare, %

- PBO QW + 26 Wk (n = 50)
- PBO QW + 52 Wk (n = 51)
- TCZ QW + 26 Wk (n = 100)
- TCZ Q2W + 26 Wk (n = 49)