SAFETY AND EFFICACY OF SUBCUTANEOUS TOCILIZUMAB IN SYSTEMIC SCLEROSIS: RESULTS FROM THE OPEN-LABEL PERIOD OF THE PHASE 3 FOCUSSED TRIAL

D. Khanna1, C. J. F. Lin2, H. Spotswood3, J. Siegele4, D. Furst4, C. Denton5
1University of Michigan, Ann Arbor, United States of America; 2Genentech, South San Francisco, United States of America; 3Roche Products Ltd, Welwyn Garden City United Kingdom; 4University of California, Los Angeles, Los Angeles, United States of America; 5University College London, London, United Kingdom

Background: The anti–interleukin-6 receptor–α antibody tocilizumab (TCZ) demonstrated skin score improvement and forced vital capacity (FVC) preservation in patients with systemic sclerosis (SSc) in a phase 2 randomized controlled trial.1-2 Data from the 48-week, double-blind (DB), placebo (PBO)-controlled period of the focussed phase 3 trial were previously presented,3 and open-label (OL) data up to week 96 are presented herein.

Objectives: To assess the long-term safety and efficacy of TCZ in SSc patients.

Methods: Adult patients with active SSc (≤60-month duration, modified Rodnan skin score [mRSS] 10-35, and elevated acute-phase reactants) treated with PBO or TCZ in the DB period received OL TCZ 162 mg SC weekly from weeks 48 to 96 in the OL period (PBO→OL TCZ→OL→OL TCZ, respectively). Exploratory analysis of data up to week 96 included no formal statistical analyses. Changes in mRSS and percent predicted FVC (ppFVC) were assessed.

Results: Overall, 92/105 TCZ (88%) and 89/107 PBO (83%) patients entered the OL TCZ treatment period at week 48, and 85/105→105→OL TCZ (81%) and 82/107 PBO→OL TCZ (77%) patients completed treatment up to week 96. Continued decline in mRSS was observed in the OL period for PBO→OL TCZ and TCZ→OL TCZ patients (Table). Change in ppFVC for patients who switched from PBO to TCZ (PBO→OL TCZ) was comparable between weeks 48 and 96 (OL period) to the change in patients who received TCZ from BL to week 48 in the DB period (Table). Rates (95% CI) of serious adverse events from weeks 48 to 96 were 15.8 (8.6, 26.5) per 100 PY for TCZ and 2.3 (0.3, 8.1) per 100 PY for PBO

Conclusion: Although OL data have been interpreted with caution, results from OL TCZ treatment show numeric improvements in mRSS and FVC preservation similar to those of the DB period, with a beneficial effect on trajectory of FVC decline in patients who switched from PBO to TCZ. Long-term safety results were consistent with the known safety profile of TCZ, and no new or unexpected events were observed.

References:

Disclosure of Interests: Dinesh Khanna Shareholder of: Eicos, Grant/research support from: NIH NIADDK, NIH NIAIMS, Consultant of: Acceleron, Actelion, Bayer, BMS, Boehringer-Ingelheim, Corbus, Galapagos, Genentech/Roche, GSK, Mitsubishi Tanabe, Sanofi-Aventis/Genezyme, UCB Pharma, Celia J. F. Lin Employee of: Genentech, Helen Spotswood Shareholder of: Roche Products Ltd, Employee of: Roche Products Ltd, Jeff Siegele Employee of: Genentech, Daniel Furst Grant/research support from: AbbVie, Actelion, Amgen, BMS, Corbus Pharmaceuticals, the National Institutes of Health, Novartis, Pfizer, and Roche/Genentech, Consultant of: AbbVie, Actelion, Amgen, BMS, Cytori Therapeutics, Corbus Pharmaceuticals, the National Institutes of Health, Novartis, Pfizer, and Roche/Genentech, Speakers bureau: CMC Connect (McCann Health Company), Christopher Denton Grant/research support from: GlaxoSmithKline, CSL Behring, and Inventiva, Consultant of: Medscape, Roche-Genentech, Actelion, GlaxoSmithKline, Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Corbus Pharmaceuticals, Acceleron, CuriZyn and Bayer

SAFETY, TARGET ENGAGEMENT, AND INITIAL EFFICACY OF AVID200, A FIRST-IN-CLASS POTENT AND ISOFORM-SELECTIVE INHIBITOR OF TGF-BETA 1 AND 3, IN PATIENTS WITH DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (dcSSC): A PHASE 1 DOSE ESCALATION STUDY

1University of Pittsburgh, Pittsburgh, United States of America; 2Hospital for Special Surgery, New York City, United States of America; 3University of Pennsylvania, Philadelphia, United States of America; 4Forbis, Montréal, Canada; 5Forbis, Austin, United States of America; 6UCCLA, Los Angeles, United States of America

Background: AVID200 is a novel, potent TGF-beta receptor ectodomain-based trap designed to selectively neutralize TGF-beta 1 and 3. These two isoforms have been implicated as central mediators of the pathogenesis of systemic sclerosis (SSc). AVID200 avoids inhibition of TGF-beta 2, the isoform that supports normal cardiac function and hematopoiesis.

Objectives: This first-in-human study (AVID200-01; NCT03831438) is a Phase 1, open label, multicenter, cohort dose-escalation trial designed to evaluate safety, tolerability, pharmacokinetic (PK) profile, pharmacodynamic (PD) effects, target engagement, and preliminary efficacy in patients with diffuse cutaneous SSc (dcSSc).

Methods: Eligible patients must have dcSSc of <5 years (y) duration and a modified Rodnan Skin Score (MRSS) ≥15. AVID200 at dose levels of 1, 3, 9, or 15 mg/kg IV is administered every 2 weeks (Q2W) for 6 weeks. Patients tolerating dosing and who have not experienced disease worsening during the initial Treatment Period may receive up to 6 additional doses Q2W (Extension Period). The ability of AVID200 to selectively sequester its target is assessed in plasma by TGF-beta quantification per ELISA and a cell-based functional read-out. Expression of biomarkers of TGF-beta inhibition and genes correlating with MRSS are assessed.

Table. Change in Efficacy From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline to Week 48</th>
<th>Baseline to Week 96</th>
<th>Week 48 to Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>TCZ</td>
<td>PBO→OL TCZ</td>
</tr>
<tr>
<td>mRSS, mean (95% CI)</td>
<td>–5.3 (–6.8, –3.7)</td>
<td>–6.7 (–8.0, –5.4)</td>
<td>–8.4 (–10.0, –6.8)</td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>ppFVC, mean (95% CI)</td>
<td>–4.1 (–5.8, –2.4)</td>
<td>–2.0 (–1.6, –1.2)</td>
<td>–3.3 (–5.1, –1.5)</td>
</tr>
<tr>
<td>(median)</td>
<td>15/91</td>
<td>5/93</td>
<td>7/97</td>
</tr>
<tr>
<td>Decline in ppFVC ≥10%, n/N (%)</td>
<td>15/91</td>
<td>5/93</td>
<td>7/97</td>
</tr>
<tr>
<td>Improvement in ppFVC, n/N (%)</td>
<td>26/91</td>
<td>43/93</td>
<td>22/79</td>
</tr>
</tbody>
</table>

*Observed data. NA, not assessed.*
Results: The first 2 dose cohorts have completed treatment: male/female 3 each, median age 61y (range 45–70), median MRSS at baseline 31 (range 23–39). Recruitment into cohort 3 is complete. AVID200 was well tolerated with no dose limiting toxicities or serious adverse events (SAEs). AEs, all considered possibly related, included single cases of Grade 1 dizziness and CPK elevation, and Grade 2 anemia. All patients demonstrated a decline in MRSS at 6 weeks by 3, 4, and 9 points in Cohort 1, and 2, 8, and 9 points in Cohort 2. Four of 6 patients demonstrated continued decrease in MRSS 12 weeks after the last dose, with all patients showing a decline in MRSS relative to baseline at the timepoint by 3, 6, and 7 points in Cohort 1 and 4, 8, and 13 points in Cohort 2. AVID200 in plasma engaged endogenous activated TGF-beta and potently neutralized signaling from exogenous TGF-beta 1 and 3, but not TGF-beta 2, across the treatment period. PD effects in skin biopsies, including expression of markers of SSC activity, TGF-beta activity, and myofibroblast-associated genes were assessed. Five of 6 patients showed decreased expression of PD biomarker genes, THBS1 and MS4A4A, comparing end of treatment biopsies to baseline, and all patients showed a decline in SERPINE1 expression, a marker gene for TGF-beta activity. Clustering of RNA-seq expression data showed close coregulation of COMP, THBS1, SERPINE1, LOXL, COL10A1, COL11A1, COL12A1, CTGF, and CDH11, suggesting that blocking TGF-beta inhibits this group of profibrotic genes. Single-cell sequencing data show that expression of these genes is upregulated by subsets of SSC fibroblasts.

Conclusion: AVID200 at doses of 1 and 3 mg/kg was well-tolerated in this first study in dcSSc patients. Evidence of anti-fibrotic effects as indicated by rapid, persistent and clinically meaningful declines in MRSS was observed in all patients, as well as AVID200 target engagement and modulation. Recruitment into additional dose and expansion cohorts is ongoing. Together, these clinical data support selective TGF-beta 1 and 3 inhibition by AVID200 as a promising therapeutic approach for dcSSc.


DOI: 10.1136/annrheumdis-2020-eular.1753