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

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Background: The anti–interleukin-6 (IL-6) receptor–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 FOCUSced phase 3 trial were previously presented,3,4 and open-label (OL) data up to week 96 are presented here.

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). 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 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 NIAID, NIH NIMMS, Consultant of: Acceleron, Actelion, Bayer, BMS, Boehringer-Ingelheim, Corbus, Galapagos, Genentech/Roche, GSK, Mitsubishi Tanabí, Sanofi-Aventis/Genzyme, UCB Pharma, Celia J. F. Lin Employee of: Genentech, Helen Spotwood Shareholder of: Roche Products Ltd, Jef Siegel 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, Cytokine 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: Medscapes, Roche-Genentech, Actelion, GlaxoSmithKline, Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Corbus Pharmaceuticals, Acceleron, Curzun and Bayer

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SAFETY, TARGET ENGAGEMENT, AND INITIAL EFFICACY OF AVI200, 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

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Background: AVI200 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). AVI200 avoids inhibition of TGF-beta 2, the isoform that supports normal cardiac function and hematopoiesis.

Objectives: This first-in-human study (AVI200-01; 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. AVI200 at dose levels of 1, 3, 9, or 15 mg/kg IV is administered every 2 weeks (Q2W) for 6 weeks (3 doses). 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 AVI200 to selectively sequester its target is assessed in plasma by TGF-beta quantification per ELISA and a cell-based functional readout. Expression of biomarkers of TGF-beta inhibition and genes correlating with MRSS are assessed.

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aObserved 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 diziness 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 12 weeks by 7, 6, and 7 points in Cohort 1 and 4, 8, and 15 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 3mg/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-escalation 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.


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EFFECTS OF NINTEDANIB IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED ILD (SSC-ILD) AND DIFFERING EXTENTS OF SKIN FIBROSIS: FURTHER ANALYSES OF THE SENSICIS TRIAL

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Background: In the SENSCIS trial, nintedanib reduced the progression of SSc-ILD compared with placebo, as shown by a significantly lower rate of decline in forced vital capacity (FVC) over 52 weeks. There was no significant difference between treatment groups in change in modified Rodnan skin score (mRSS) at week 52. An mRSS of 18–25 has been proposed as an upper cut-off to enrich a cohort for progression-naive patients. Progression of skin fibrosis has been associated with later progression of ILD.

Objectives: To assess the effects of nintedanib on the rate of FVC decline and change in mRSS in the SENSCIS trial in subgroups by mRSS <18 and ≥18 at baseline.

Methods: Patients with SSC-ILD with onset of first non-Raynaud symptom <7 years before screening and ≥10% fibrosis of the lungs on a high-resolution computed tomography scan were randomised to receive nintedanib or placebo. We analysed the rate of decline in FVC (ml/year) over 52 weeks and the change from baseline in mRSS at week 52 in subgroups by mRSS (<18; ≥18) at baseline.

Results: In the nintedanib and placebo groups, respectively, 219/288 (76.0%) and 226/288 (78.5%) patients had mRSS <18 at baseline. Compared with those with mRSS <18, patients with mRSS ≥18 had a lower mean FVC % predicted (68.3% vs 73.7%) and greater proportions were taking mycophenolate at baseline (58.1% vs 45.6%), were anti-topoisomerase I antibody positive (67.4% vs 58.7%) and had diffuse cutaneous SSC (100% vs 1738%). The mean (SE) annual rate of decline in FVC in the placebo group was numerically greater in patients who had mRSS <18 than mRSS ≥18 at baseline (<13.7 [9.2]) ml/year vs -8.14 [15.4] ml/year). The effect of nintedanib vs placebo on reducing the annual rate of decline in FVC was numerically more pronounced in patients with mRSS ≥18 (difference: 88.7 [9.3] ml/year [95% CI 7.7, 169.8]) than mRSS <18 (difference: 26.4 [6.5] ml/year [95% CI 16.8, 69.6]) at baseline, but statistical testing did not indicate heterogeneity in the treatment effect of nintedanib between subgroups (p<0.18 for treatment-by-time-by-subgroup interaction). In the nintedanib and placebo groups, respectively, changes in mRSS at week 52 were -2.2 (0.3) and -2.1 (0.3) (difference -0.1 [95% CI -0.7, 0.7]) in patients with mRSS <18 at baseline and -2.1 (0.7) and -1.6 (0.7) (difference -0.6 [95% CI 2.1, 10]) in patients with mRSS ≤18 at baseline (p=0.62 for treatment-by-visit-by-subgroup interaction).

Conclusion: In the placebo group of the SENSCIS trial, the rate of decline in FVC over 52 weeks was numerically greater in patients with mRSS ≥18 vs <18 at baseline, while reductions in mRSS were similar. A lower rate of FVC decline was observed in patients treated with nintedanib than placebo both in patients with mRSS ≥18 and <18 at baseline.

Figure. Rate of decline in FVC over 52 weeks in subgroups by mRSS <18 and ≥18 at baseline in the SENSCIS trial.

mRSS <18

mRSS ≥18

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