Figure 2. Percentage of progressors in inception cohort versus percentage of progressors in non-inception cohort after one year of follow-up stratified for immunosuppressive treatment (n=250 non-inception cohort, n=106 inception cohort).

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THU0328

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

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Background: The anti-interleukin-6 (IL-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 focuSSced 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 $\rightarrow$ OL TCZ and TCZ $\rightarrow$ 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 TCZ $\rightarrow$ OL TCZ (81%) and 82/107 PBO $\rightarrow$ OL TCZ (77%) patients completed treatment up to week 96. Continued decline in mRSS was observed in the OL period for PBO $\rightarrow$ OL TCZ and TCZ $\rightarrow$ OL TCZ patients (Table). Change in ppFVC for patients who switched from PBO to TCZ (PBO $\rightarrow$ 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 $\rightarrow$ OL TCZ patients, 14.8 (7.9, 25.3) per 100 PY for PBO $\rightarrow$ OL TCZ patients, and 15.4 (11.0, 20.9) for all TCZ exposure over 96 weeks (n = 193). Rates (95% CI) of serious infections were 2.3 (0.3, 8.1) per 100 PY for TCZ $\rightarrow$ OL TCZ patients, 3.4 (0.7, 10.0) per 100 PY for PBO $\rightarrow$ OL TCZ patients, and 3.0 (1.3, 5.9) for all TCZ exposure over 96 weeks. One death occurred during the OL period in each arm.

Conclusion: Although OL data have to be 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.

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THU0329

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

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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 (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 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

	Baseline to Week 48		Baseline to Week 96		Week 48 to Week 96	
	PBO	TCZ	PBO $\rightarrow$ OL TCZ	TCZ $\rightarrow$ OL TCZ	PBO $\rightarrow$ OL TCZ	TCZ $\rightarrow$ OL TCZ
mRSS, mean (95% CI) ^a	-5.3 (-6.9, -3.7) n = 92	-6.7 (-8.0, -5.4) n = 97	-8.4 (-10.0, -6.8) n = 83	-9.6 (-10.9, -8.4) n = 85	-2.5 (-3.3, -1.6) n = 82	-2.3 (-3.2, -1.5) n = 85
ppFVC, mean (95% CI) [median]	-4.1 (-5.8, -2.4) [-3.9] n = 92	-0.2 (-1.6, 1.2) [-0.7] n = 94	-3.3 (-5.1, -1.5) [-3.1] n = 79	-0.5 (-2.4, 1.3) [-1.4] n = 84	0.6 (-0.7, 1.9) [0.3] n = 78	-0.3 (-1.7, 1.1) [0.0] n = 82
Decline in ppFVC $\geq 10\%$, n/N (%) ^a	15/91 (16.5)	5/93 (5.4)	14/79 (17.7)	11/84 (13.1)	NA	NA
Improvement in ppFVC, n/N (%) ^a	26/91 (28.6)	43/93 (46.2)	22/79 (27.8)	35/84 (41.7)	NA	NA

^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 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 this timepoint by 7, 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 potentially 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 and extension 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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THU0330

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 SENSICIS 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 skin-progressive 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 SENSICIS 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 37.8%). 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 (-131.7 [29.2] mL/year vs -81.4 [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 mL/year [95% CI 7.7, 169.8]) than mRSS <18 (difference: 26.4 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) (Figure). 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 -1.0, 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, 1.0]) in patients with mRSS ≥18 at baseline (p=0.62 for treatment-by-visit-by-subgroup interaction).

Conclusion: In the placebo group of the SENSICIS trial, the rate of decline in FVC over 52 weeks was numerically greater in patients with mRSS ≥18 than <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 SENSICIS trial

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