Results: 20/22 (91%) eligible subjects enrolled in the OLE, following a mean interval of 31 weeks from the end of Part A, during which they continued to receive standard-of care treatments, to the start of the OLE during which lenabasum 20mg BID was added. 17/20 (85%) subjects were on stable baseline immunosuppressive drugs. At the time of this data cut-off, 17 subjects were still enrolled, 17 had completed 140 months (2.7 years), and 15 had completed 156 months (3 years) of OLE dosing. All OLE subjects experienced at least 1 adverse event (AE), with 118 AEs during the OLE through Dec 2020. Most AEs were mild ($n = 111$, 94%), with 2 severe AEs (fatigue and metastatic prostate cancer) considered unrelated to lenabasum. AEs occurring in $\geq 3/20$ OLE subjects were: URI ($n = 5$); fatigue ($n = 4$); nausea ($n = 3$); common cold ($n = 3$); UTI ($n = 3$); and DM flare ($n = 3$). No serious AEs related to lenabasum have been reported in this OLE to date. No subject discontinued the OLE because of an AE related to lenabasum. Improvement was seen in multiple physician- and patient-reported efficacy outcomes. CDASI activity score improved through the first 15 months of lenabasum treatment in the OLE and remained stable thereafter, with an improvement of ~ 20 points from the beginning of the study maintained from Month 15 through Year 3 in the OLE. CDASI damage score increased through the first year of the OLE, even though skin activity was decreasing, but lessened thereafter, returning after 3 years to about the same level it was at the beginning of the OLE. Other outcomes shown in Figure 1 followed the same general pattern as CDASI activity score, with improvement through the first 12-16 months of the OLE, then stability thereafter. Of note, 2 subjects had disease flares shortly after stopping lenabasum for conclusion of the OLE.

Conclusion: Lenabasum continues to have a favorable safety and tolerability profile in the OLE of the Phase 2 JBT101-DM-001 with no serious AEs or study discontinuations related to lenabasum. The CDASI activity score and multiple other physician and patient-reported outcomes improved and have remained stable, showing durability of improvement in these patients with refractory skin disease. Skin damage was reversible and began to improve once skin activity stabilized. The limitations of attributing this improvement to lenabasum in the setting of open-label dosing is acknowledged. These data support further testing of lenabasum for the treatment of DM, and a Phase 3 study of lenabasum in DM is ongoing.

Figure 1. Change from Baseline in Selected Efficacy Outcomes in OLE of Phase 2 Trial JBT101-DM-001

Disclosure of Interests: Victoria Werth Grant/research support from: Investigator for Corbus Pharmaceuticals and received funding to conduct trials, Josef Concha: None declared, Julie Burroughs: None declared, Joyce Okawa: None declared, Rui Feng: None declared, Anisha Jobanputra: None declared, Robert Borucki: None declared, Kathleen Hally Employee of: Employee of Corbus Pharmaceuticals, Emily Hejazi: None declared, Michael Tillinger Employee of: Employee of Corbus Pharmaceuticals, Scott Constantine Employee of: Employee of Corbus Pharmaceuticals, Nancy Dgetluck Employee of: Employee of Corbus Pharmaceuticals, Barbara White Employee of: Employee and stockholder of Corbus Pharmaceuticals

DOI: 10.1136/annrheumdis-2021-eular.2048

POS0316

MODELLING SHORT-TERM FVC CHANGES FROM SENSICIS TO LONG-TERM FVC COURSE IN SSC-ILD DEMONSTRATES CLINICALLY MEANINGFUL REDUCTION OF FVC DECLINE AND SURVIVAL BENEFITS

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Background: Nintedanib has shown to slow FVC decline by 41ml over 52 weeks in systemic sclerosis-associated interstitial lung disease (SSc-ILD). However, the long-term effect of nintedanib treatment on ILD progression and mortality in SSc patients is so far unknown.

Objectives: Here, the 52-week treatment efficacy of nintedanib was modeled and extrapolated on the long-term FVC course and survival in SSc-ILD patients from the European Scleroderma Trial and Research (EUSTAR) database.

Methods: SSc patients from the EUSTAR database fulfilling the inclusion criteria of the SENSICIS trial (SSc classification criteria, ILD confirmed by imaging, disease duration of <7 years, FVC $\geq$ 40%pred, diffusion capacity of the lung for carbon monoxide (DLCO) 30-89%pred) and matched for baseline characteristics as well as matched for the 52-week FVC change of SENSICIS patients were included ($n=236$). Linear mixed models including time, risk factors at baseline (sex, age, dyspnea class, DLCO%, CRP, modified Rodnan skin score, SSc subtype, SSc auto-antibodies, disease duration, synovitis and muscle weakness) were used to estimate the natural FVC course over time. On this natural course of FVC, the observed effect from the SENSICIS trial representing the absolute 52-week difference of FVC decline between the nintedanib and the placebo group was applied as continuous annual effect (SENSICIS effect model). Survival was estimated for both the natural course as well as the SENSICIS effect model using Cox regression.

Results: Of the 236 included patients, 75% were females, 65% had diffuse cutaneous SSc. Mean age was 50.6 years, mean FVC 78.2%pred and DLCO 56.3%pred at time of inclusion. Mean FVC change after 12 $\pm$ 3 months was -2.3 $\pm$ 6.9%pred. These parameters were largely similar to the characteristics of the SENSICIS population.

In the longitudinal follow up of this population, the natural course of FVC showed a total FVC decline of -16.3%pred over 5 years. With assumed SENSICIS effects (effects of nintedanib treatment reported in SENSICIS), the 5-year FVC decline was reduced to -10.3%pred (Figure 1).

The reduced FVC progression translated into an improved survival. The natural 5-year survival of this SSc-ILD population was 88.2%. When extrapolating also a severe FVC decline early in the course, frequently terminated by early mortality of SSc patients excluding them from long-term outcome assessment, the estimated 5-year survival was reduced to 81.6%. When the SENSICIS effects on

FVC were considered, the 5-year extrapolated survival was increased to 86.3% (Figure 2).

Conclusion: Long-term experience of nintedanib treatment in SSc-ILD patients is lacking so far, therefore we modeled and extrapolated the 52-week treatment efficacy of nintedanib on the long-term FVC course and survival in SSc-ILD patients from the EUSTAR database. We could demonstrate a significant reduction of FVC decline by extrapolating the annual treatment effects of nintedanib from the SENSICIS trial from 1 to 5 years in EUSTAR. Translating these reductions of FVC decline into survival, the 5-year mortality rate was reduced from 18% to 13%.

Disclosure of Interests: Anna-Maria Hoffmann-Vold Speakers bureau: Boehringer Ingelheim, Actelion, Roche, Merck Sharp & Dohme, Lilly, Consultant of: Actelion, Boehringer Ingelheim, Roche, Bayer, Merck Sharp & Dohme, ARXX, Lilly and Medscape, Grant/research support from: Boehringer Ingelheim, Dörte Huscher: None declared, Paolo Airò Speakers bureau: Boehringer Ingelheim, Consultant of: Bristol-Myers-Squibb, Novartis, Elisabetta Zanatta Speakers bureau: Boehringer Ingelheim, Actelion, GSK, Paid instructor for: GSK, Consultant of: Boehringer Ingelheim, GSK, Patricia Carreira Speakers bureau: Actelion, Boehringer Ingelheim, Janssen, GSK, Paid instructor for: Boehringer Ingelheim, Consultant of: AbbVie, Boehringer Ingelheim, VivaCell, Emerald Health Pharmaceuticals, Gesynta Pharma, Sanofi Genzyme, Grant/research support from: Roche, GSK, Yannick Allanore Consultant of: Honorarium received from Boehringer, Medsenic

Sanofi, Menarini, Grant/research support from: Grants received from Alpine, Ose Immunogenetics, Ulf Müller-Ladner Speakers bureau: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Alessandro Giollo: None declared, Maria Rosa Pozzi: None declared, CAROLINA SOUZA MULLER Speakers bureau: Boehringer Ingelheim, Janssen, Roche, LIBBS, Bristol-Myers-Squibb, Radim Bečvář Consultant of: Actelion, Boehringer Ingelheim, Michele Iudici: None declared, Dominik Majewski Speakers bureau: Boehringer Ingelheim - 2 x paid as a speaker, Armando Gabrielli Grant/research support from: Pfizer, CSL Behring, Margarida Alves Employee of: Boehringer Ingelheim, Nils Schoof Employee of: Boehringer Ingelheim International GmbH, Oliver Distler Speakers bureau: Boehringer Ingelheim, Medscape, IQone, Roche, Consultant of: AbbVie, Acceleron Pharma, Amgen, AnaMar, Arxx Therapeutics, Baeon Discovery, Blade Therapeutics, Bayer, Boehringer Ingelheim, ChemomAb, Corbus Pharmaceuticals, CSL Behring, Galapagos NV, Glenmark Pharmaceuticals, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, IQvia, Italfarmaco, Kymera Therapeutics, Lilly, Medac, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Serodapharm, Topadur, Target Bioscience and UCB, Grant/research support from: Kymera Therapeutics, Mitsubishi Tanabe

DOI: 10.1136/annrheumdis-2021-eular.2522

POS0317

THE PERFORMANCE OF DIFFUSING CAPACITY FOR MONOXIDE CARBON (DLCO) AND FORCED VITAL CAPACITY (FVC) IN PREDICTING THE ONSET OF SYSTEMIC SCLEROSIS (SSC)-INTERSTITIAL LUNG DISEASE (ILD) IN THE EUROPEAN SCLERODERMA TRIALS AND RESEARCH (EUSTAR) DATABASE

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Background: In SSc, ILD is a major cause of morbidity and mortality. High resolution computed tomography (HRCT) is the gold standard for the diagnosis. Predictors of ILD onset are eagerly awaited to improve SSc-ILD management. Pulmonary function test (PFTs) are routinely performed to measure lung function changes.

Objectives: Our aim was to investigate the performance of DLCO (diffusing capacity of lung carbon monoxide) and FVC (forced vital capacity) in predicting the development of SSc-ILD.

Methods: The longitudinal data of DLCO, FVC and ILD on HRCT of SSc patients from the EUSTAR database were evaluated at baseline (t_0), after 12 (± 4) (t_1) and 24 (± 4) (t_2) months. Patients with negative HRCT for any sign of ILD both at t_0 and t_1 were included. Patients who presented or developed pulmonary hypertension during the study period were excluded. At baseline, demographic data, disease duration from Raynaud's onset, disease subsets, autoantibodies and other laboratory and instrumental data were recorded.

Results: 474/17805 patients were eligible for the study (403 females, 71 males): 26.0% dcSSc, 58.3% lcSSc, 220 (48.0%) patients with positive anticentromere antibodies (ACA) and 117 (25.4%) with positive antitopoisomerase I antibodies (Topo-I abs). Among all enrolled patients, 46 (9.7%) developed HRCT signs of ILD at t_2 . Patients with Topo-I abs showed an association with ILD development at t_2 (16.7% vs 7.8%, $p=0.0031$), contrarily ACA positive patients were negatively associated with ILD appearance after 2 years of follow-up (4.4% vs 14.4%, $p=0.0001$). Positive t_2 HRCT patients had a significant lower value of DLCO and FVC at all three assessments when compared to patients with a negative HRCT at t_2 (Table 1) and both t_0 DLCO and FVC values negatively correlated with ILD development (Table 1). The mean t_0 to t_1 change (Δ) of DLCO in patients with negative t_2 HRCT and positive t_2 HRCT were $-0.5 (\pm 12.6)$ and $-1.0 (\pm 15.1)$, respectively. The mean t_0 to t_1 Δ FVC in patients with negative t_2 HRCT and positive t_2 HRCT were $-0.2 (\pm 10.6)$ and $0.1 (\pm 11.5)$, respectively. None of them predicted the appearance of ILD at t_2 (ADLCO: OR (IC) 0.997 (0.97-1.02), $p=0.8024$; Δ FVC OR (IC) 1.002 (0.97-1.03), $p=0.8664$). The data showed an association between t_0 DLCO value <80% and ILD appearance after 2 years of follow-up [OR(IC): 3.09 (1.49-6.40), $p=0.0023$]. Such association was not observed for t_0 FVC value <80% [OR(IC): 1.95 (0.81-4.68), $p=0.1329$]. The predictive capability of t_0 DLCO <80% was moderate but stronger than FVC <80% [AU ROC: 0.62 (0.56-0.69), 0.53 (0.48-0.59) respectively, $p=0.0205$].

Conclusion: Our data suggest that an impaired baseline DLCO (<80%) may have a predictive value for the development of ILD on HRCT after 2 years of follow-up. Further rigorous prospective studies are warranted to understand the role of DLCO evaluation in the course of SSc.

Table 1. DLCO and FVC values at t_0 , t_1 and t_2 values in patients with positive or negative HRCT for ILD at t_2 and their statistical differences.

	Patients without ILD at t_2 (mean $\pm$ SD)	Patients with ILD at t_2 (mean $\pm$ SD)	OR (95%CL)	p-value
DLCO at t_0	79.0 $\pm$ 16.6	69.9 $\pm$ 17.4	0.97 (0.95 - 0.99)	0.0006
DLCO at t_1	78.4 $\pm$ 16.8	68.9 $\pm$ 18.6	0.97 (0.95 - 0.98)	0.0005
DLCO at t_2	78.0 $\pm$ 17.0	65.1 $\pm$ 19.1	0.95 (0.93 - 0.97)	<0.0001
FVC at t_0	102.2 $\pm$ 17.3	94.6 $\pm$ 16.2	0.97 (0.96 - 0.99)	0.0052
FVC at t_1	101.9 $\pm$ 17.9	94.7 $\pm$ 16.5	0.98 (0.96 - 0.99)	0.0092
FVC at t_2	101.6 $\pm$ 17.6	94.5 $\pm$ 20.0	0.98 (0.96 - 1)	0.0126

Disclosure of Interests: Gemma Lepri: None declared, Cosimo Bruni Speakers bureau: CB reports personal fees from Actelion, personal fees from Eli Lilly, Grant/research support from: CB reports personal fees from Actelion, personal fees from Eli Lilly, grants from European Scleroderma Trial and Research (EUSTAR) group, grants from New Horizon Fellowship, grants from Foundation for Research in Rheumatology (FOREUM), grants from Fondazione Italiana per la Ricerca sull'Artrite (FIRA), outside the submitted work, Lorenzo Tofani: None declared, Alberto Moggi Pignone: None declared, Martina Orlandi: None declared, Tomasetti Sara Speakers bureau: Speaker's fees for Roche and Boehringer Ingelheim,