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Safety and Tolerability of Pirfenidone in Patients with Systemic Sclerosis Interstitial Lung Disease

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Interstitial lung disease (ILD) is a common and serious complication of systemic sclerosis (SSc). Pirfenidone, a novel antifibrotic agent, has been shown to be safe and effective in the treatment of idiopathic pulmonary fibrosis (IPF). The LOTUSS study was designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD.

Methods: This is an open-label, 16-week study. Patients were randomized to a 2- or 4-week titration to the target dose of 2403 mg/day. Eligibility required a diagnosis of SSc ≤7 years from first non-Raynaud's symptom, HRCT-confirmed ILD, FVC ≥50% and DL_{CO} ≥40%, absence of clinically significant pulmonary hypertension or severe GERD. Stable treatment with mycophenolate mofetil (MMF) or oral cyclophosphamide was permitted. Safety assessments included collection of treatment emergent adverse events (TEAEs), vital signs, ECGs and laboratory tests. Though the study was not designed or powered to evaluate efficacy, FVC %-predicted, DL_{CO} %-predicted, modified Rodnan skin score (mRSS), Mahler BDI/TDI, and UCLA SCTC GIT 2.0 were recorded at baseline and 4 months.

Results: Of the 63 patients enrolled, the mean (SD) age was 50.6 (12.3) years; the majority were female (82.5%) and white (76.2%). The mean (SD) SSc duration was 38.3 (26.0) months. Forty patients (63.5%) were on MMF and the rest (36.5%) were not receiving any immunosuppressants. The mean (SD) mRSS, %FVC and $\%DL_{CO}$ at

baseline were 11.4 (9.6), 76.0 (14.2) and 59.7 (16.5), respectively.

The frequency and type of TEAEs were
similar for both titration groups. The safety results are summarized below. No clinically significant changes in vital signs, ECGs, or laboratory tests were observed.

At week 16, the median change from baseline
in %FVC was -0.5% (range -42% to 12%); 10 patients (16.7%) had an increase ≥5% whereas 5 (8.3%) had a decrease >5% at week 16. Median change from baseline in $\%DL_{CO}$ was 1.5% (range -24.0% to 40.0%); 19 subjects (31.7%) had an increase ≥5% vs. 10 (16.7%) had a decrease >5% at week 16. Minor changes (mean±SD) were observed in Mahler TDI (1.0±3.41) and mRSS (-0.4±3.71). No change was noted in the GI symptoms on UCLA SCTC GIT 2.0.

Conclusion:
In the 16-week, open-label trial of pirfenidone in SSc-ILD, pirfenidone was safe and generally well-tolerated in SSc-ILD patients, despite pre-existing co-morbidities, including underlying GI disease, and concomitant use of MMF. The AEs were expected and consistent with those previously seen in IPF trials. The data support further investigation of pirfenidone in SSc-ILD.

Safety Summary	
	All Patients (N=63)
Total Number of TEAEs	521
No. of Patients with Any TEAEs	61 (96.8%)
No. of Patients with TEAEs by Maximum Intensity	
Mild TEAEs	19 (30.2%)
Moderate TEAEs	30 (47.6%)
Severe TEAEs	12 (19.0%)
Most Common TEAEs (>=10% of Patients)	
NAUSEA	31 (49.2%)
HEADACHE	28 (44.4%)
FATIGUE	23 (36.5%)
DIARRHEA	19(30.2%)
VOMITING	18(28.6%)
COUGH	14(22.2%)
GASTROESOPHAGEAL REFLUX DISEASE (GERD)	13(20.6%)
RASH	13(20.6%)
DIZZINESS	10(15.9%)
ARTHRALGIA	9(14.3%)
BACK PAIN	8(12.7%)
DYSPEPSIA	8(12.7%)
PRURITUS	8(12.7%)
ANOREXIA	7(11.1%)
ASTHENIA	7(11.1%)
CONSTIPATION	7(11.1%)
DYSPNEA	7(11.1%)
INSOMNIA	7(11.1%)
STOMACH DISCOMFORT	7(11.1%)
No. of Patients with Serious TEAEs	3 (4.8%)
Serious TEAEs	
SMALL INTESTINAL OBSTRUCTION	1 (1.6%)
BRONCHITIS	1 (1.6%)
PULMONARY HYPERTENSION	1 (1.6%)
WORSENING ILD	1 (1.6%)
No. of Patients Who Discontinued Study Due to TEAEs	6 (9.5%)
TEAEs Leading to Study Discontinuation	
DRUG HYPERSENSITIVITY	1 (1.6%)
WORSENING FIBROMYALGIA PAIN	1 (1.6%)
PULMONARY HYPERTENSION	1 (1.6%)
PHOTOSENSITIVITY REACTION	1 (1.6%)
RASH	2 (3.2%)

Disclosure: D. Khanna, Bristol Myers-Squibb, EMD Serono, Genentech/Roche, NIH/NIAID-ACE, NIH/NIAMS-K24, PCORI and Scleroderma Foundation, 2,Bayer, Biogen, Cytori, EMD Serono, Forward, Genentech/Roche, Gilead, Lycera and Seattle Genetics, 5; **C. Albera**, InterMune, Roche,

GlaxoSmithKline, Boehringer Ingelheim, and Baye., 5; **A. Fischer**, Roche-Genentech, 2,Actelion, Boehringer Ingelheim, Bristol-Myers Squibb, Roche-Genentech, Gilead, GlaxoSmithKline and Seattle Genetics, 5; **J. R. Seibold**, Actelion, Aires, Apricus/Nexmed, Bayer, Boehringer Ingelheim, Covis, Cellgene, DART, Eiccose, Eiger, EMD Serono, FibroGen, Gilead, InterMune, Novartis, Pfizer, Sanofi-Aventis, Sigma Tau and United Therapeutics, 5; **N. A. Khalidi**, None; **G. Raghu**, Roche-Genentech and Boehringer Ingelheim, 5; **L. Chung**, Gilead, 4; **E. Schiopu**, InterMune, 2; **D. Chen**, None; **E. Gorina**, InterMune Inc, 3.

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