European Respiratory Society
Annual Congress 2012

Abstract Number: 1993

Publication Number: P1778

Abstract Group: 1.5. Diffuse Parenchymal Lung Disease

Keyword 1: Idiopathic pulmonary fibrosis **Keyword 2:** Treatments **Keyword 3:** Lung function testing

Title: MUSIC: Efficacy and safety of macitentan in idiopathic pulmonary fibrosis (IPF)

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Body: Endothelin-1 may contribute to IPF pathophysiology. The prospective double-blind Macitentan USe in an IPF Clinical (MUSIC) trial (NCT00903331) investigated the endothelin receptor antagonist macitentan in adults with IPF of <3 years duration and a histological pattern of usual interstitial pneumonia on surgical lung biopsy. Patients were randomised 2:1 to macitentan (10 mg once daily) or placebo. The primary objective was to show that from baseline up to Month 12 macitentan positively affects forced vital capacity (FVC) versus placebo. Baseline demographics and characteristics were comparable between treatment arms.

	Macitentan, n=119	Placebo, n=59
Males, n (%)	84 (70.6)	37 (62.7)
Mean age±SD, years	65.1±7.9	64.5±6.3
Mean FVC±SD, % predicted	76.5±15.6	74.8±14.6
Mean corrected DLco±SD, % predicted	47.8±13.4*	45.6±11.2

*n=115; DLco, carbon monoxide diffusing capacity; SD, standard deviation

Mean (range) exposure to macitentan was 14.3 (0.0–24.6) months and to placebo was 15.4 (6.3–24.3) months. Median (95% confidence limit) change in FVC was −0.20 L (−0.29 to −0.16) for macitentan and −0.20 L (−0.28 to −0.13) for placebo; ie. no treatment effect on FVC was observed. No difference in time to IPF worsening or death was observed. Adverse events in ≥10% of macitentan-treated patients with a ≥5% difference versus placebo comprised peripheral oedema, anaemia (both favoured placebo), cough (favoured macitentan). Hepatic aminotransferase elevations >3× upper limit of normal occurred in 3.4% of macitentan recipients and 5.1% of placebo recipients. In summary, the primary objective was not met.

Long-term macitentan exposure was well tolerated with rates of elevated hepatic aminotransferases comparable to placebo.