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Title: Elevated serum LOXL2 levels are associated with rapid disease progression in idiopathic pulmonary fibrosis (IPF)

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Body: Background: LOXL2, expressed in fibrotic lung, plays a crucial role in matrix remodeling and fibrogenesis. We hypothesized that elevated serum LOXL2 levels are associated with rapid IPF disease progression. Methods: Baseline serum samples were collected prior to treatment randomization at selected U.S. clinical trial sites for ARTEMIS-IPF. LOXL2 levels were measured using proprietary anti-human-LOXL2 antibodies. Progression free survival ([PFS] lung function decline, respiratory hospitalizations [RH] and death) served as the primary endpoint. Results: Subjects with (n=69) and without (n=423) serum samples had similar baseline IPF severity. Among subjects with detectable LOXL2 (n=67), the median LOXL2 level was 315.4pg/ml (IQR 144.5-752.4 pg/ml). Although subjects randomized to receive ambrisentan (n=49) had more severe IPF and higher LOXL2 levels than placebo treated subjects (mean 902.8pg/ml±1172 vs 294pg/ml±288, p=0.026), LOXL2 levels and IPF severity did not correlate. In multivariate analyses that included treatment assignment, 6-minute walk distance and composite physiologic index, high LOXL2 levels (>800pg/ml), in comparison to low LOXL2 levels (≤800pg/ml), were associated with increased risk for disease progression (hazard ratio [HR] 4.95, 95% confidence interval [CI] 1.52-16.18, p=0.008), lung function decline (HR 7.36, 95% CI 1.16-46.74, p=0.034, and RHs (HR 4.85, 95% CI 1.09-21.68, p=0.039). Conclusion: High baseline serum LOXL2 levels are associated with rapid IPF progression and may reflect disease activity, not severity. Due to potential confounding effects of ambrisentan, these results need to be replicated in other IPF populations.