PIPE-791 and BMS-986278: Two Lysophosphatidic Acid Receptor 1 (LPA1) Antagonists with Distinct Lung Occupancy Profiles and Vascular Effects

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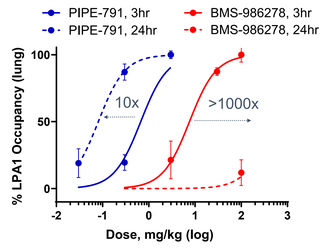
Background

- A link between LPA1 and pulmonary fibrosis was first described by Tager et al., (2008) prompting the discovery of AM152, a first-generation LPA1 antagonist
- Renamed BMS-986020, this compound provided preliminary evidence of efficacy in IPF, but development was halted due to unexpected hepatobiliary toxicity
- Admilpirant (BMS-986278), a second-generation antagonist, resolved liver toxicity but requires twice daily dosing and has shown signs of hypotension
- **We present PIPE-791, a next generation LPA1 receptor antagonist, offering superior target occupancy with once-daily dosing and reduced LPA-induced hemodynamic effects, potentially enhancing patient safety**

Methods

- *In vivo* lung LPA1 occupancy was evaluated following orally dosed PIPE-791 or BMS-986278 using a filtration method of homogenized tissue after intravenous [3H]-PIPE-497, an LPA1-selective radioligand
- *In vitro* vascular cell responses and receptor Kinetis were determined using primary human aortic smooth muscle cells (hASMC) cultured and loaded with calcium dye. Inhibition curves were generated following LPA challenge.
- *In vivo* vascular responses were recoded using laser speckle contrast imaging focused on surface blood flow. Mice received an intravenous bolus injection of either LPA or vehicle. Subsequent surface blow flow effects were monitored and graphed.

LPA1 Receptor Occupancy

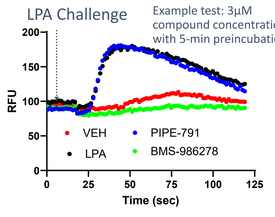


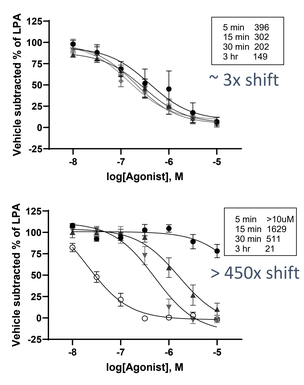
	3hr	24hr
PIPE-791 (ED_{50}, mg/kg)	**0.4**	**0.1**
BMS-986278 (ED_{50}, mg/kg	**7.5**	**>100**

- PIPE-791 shows sustained occupancy from 3 - 24-hours allowing once daily dosing
- BMS-986278 shows large drop in occupancy over time suggesting the need for twice daily dosing
- **PIPE-791 clinical efficacious dose prediction <10 mg (QD)** (versus BMS-986278, 60 - 120 mg (BID))

LPA-evoked Vascular Response *in vitro* and *in vivo*

In vitro hASMC ca^{++} mobilization

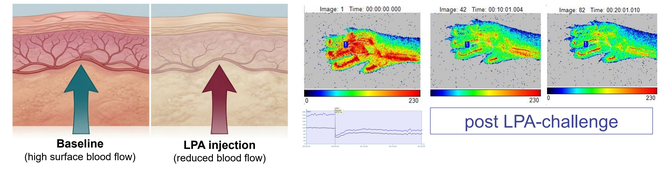




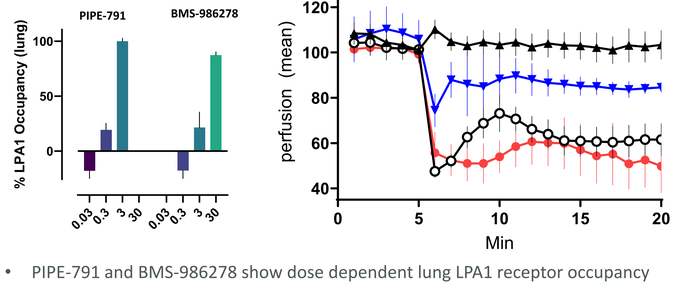
- PIPE-791 shows slow inhibition kinetics compared to BMS-986278
- hAVSMC assay may have predictive validity for clinical BP observations

Summary Table	hASMC Kinetics	BP effects reported
PIPE-791	**Slow**	**No**
BMS 986278	**Rapid**	**Yes**
BMS 986020	**Rapid**	**Yes**
AMG 670	**Rapid**	**Yes**

In vivo microcirculation blood flow



3 mg/kg (PIPE-791) and 30 mg/kg (BMS278) showing comparable LPA1 target occupancy were dosed 30 minutes prior to LPA challenge



- PIPE-791 and BMS-986278 show dose dependent lung LPA1 receptor occupancy
- At pharmacological equivalent doses, BMS-986278 [but not PIPE-791] inhibits the rapid LPA-induced vascular constriction response shown by laser doppler

Summary and Conclusion

PIPE-791 demonstrates superior lung receptor occupancy with sustained coverage. This effect is consistent with the long receptor residence time shown for PIPE-791 in binding studies. PIPE-791 also showed delayed and blunted LPA-induced vascular responses *in vitro* and *in vivo*. Although speculative, the unique pharmacology of PIPE-791 may mitigate rapid hemodynamic responses observed clinically with prior LPA1 antagonists offering a safer, once daily, therapeutic for patients with pulmonary fibrosis.

1. Tager AM, LaCamera P, Shea BS, Campanella GS,et al. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. Nat Med. 2008 Jan;14(1):45-54.
2. L. Sivaraman, , M. Gill b , D.M. Nelson, K.D. Chadwick. Structure dependence and species sensitivity of in vivo hepatobiliary toxicity with lysophosphatidic acid receptor 1 (LPA1) antagonists. Toxicology and Applied Pharmacology 438 (2022) 115846
3. Corte TJ, Behr J, Cottin V, Glassberg MK, et al. Efficacy and Safety of Admilparant, an LPA1 Antagonist, in Pulmonary Fibrosis: 2. A Phase 2 Randomized Clinical Trial. Am J Respir Crit Care Med. 2025 Feb;211(2):230-238.