The non-prostanoid IP receptor agonist, APD811 has potent antiproliferative and vasorelaxant properties in human pulmonary artery

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Introduction: APD811 is a non-prostanoid IP receptor agonist with a long plasma half-life (~ 24hr) in clinical development by Arena for pulmonary arterial hypertension (PAH). The aim was to compare functional effects of APD811 in distal human pulmonary smooth muscle cells (PASMCs) and arteries (PAs) with other prostacyclin mimetics already licensed for PAH.

Methods: PASMCs from PAH patients were grown in 9% serum, treated with agonists±1 µM RO-1138452 (IP receptor antagonist) for 1 or 96hr and cAMP (ELISA) and cell proliferation (MTS) assessed. Distal PAs from control patients were mounted in a myograph and constricted with U46619 (thromboxane mimetic; 100nM). The concentration (EC_{50}) producing the half maximal response (E_{Max}) was determined.

Results: Iloprost APD811, MRE-269 (selexipag metabolite) and treprostinil increased cAMP (EC_{50} 17, 252, 340, 550 nM, respectively). E_{Max} was lower ($P<0.001$) for all three agents compared with treprostinil. In proliferation assays, APD811 was 10 fold more potent (14 nM) than MRE-269 (145 nM) and E_{Max} lower for both compared to treprostinil (57% versus 89%). RO-1138452 abolished agonist-induced cAMP generation and the antiproliferative effects of APD811 and MRE-269. In PAs, APD811 produced a significantly ($P<0.001$) greater relaxation (E_{Max} 98%) compared to iloprost (E_{Max} 84%), treprostinil (E_{Max} 71%) or MRE-296 (E_{Max} 59%) and was more potent (EC_{50} 449nM *versus* 1579nM) than MRE-269.

Conclusions: APD811 and MRE-269 behave as selective, but partial IP receptor agonists, though APD811 produced superior effects to MRE-269 in all assays and had a favourable vasodilator profile compared with iloprost and treprostinil.