Treatment with MRGPRX2 Antagonist EP262 Potently Inhibits Mast Cell Degranulation

Presented at the 6th GA²LEN Global Urticaria Forum, December 7-8, 2022 in Berlin, Germany

Authors: Joshua Wollam[1], Michelle Solomon[1], Christiane Villescaz[1], Marion Lanier[1], Jennifer Brooks[1], Andrew Kim[1], Samantha Anderson[1], Corinne Pisacane[1], David Freeman[1], Alexis Vasquez[1], Brittney Charlot[1], Alan Vest[1], Jim Napora[1], Christine Cavarlez[1], Lisa Dvorak[1], Brandon Selfridge[1], Liming Huang[1], Marcos Sainz[1], Andres Nevarez[1], Gregg Timony[1], Esther Martinborough[1], Veena Viswanath[1], Marcus Boehm[1]

[1]Escient Pharmaceuticals, Inc., San Diego, CA, USA

Rationale: Mas-Related G-Protein Coupled Receptor X2 (MRGPRX2; mouse ortholog Mrgprb2) is a promiscuous receptor expressed on mast cells that mediates mast cell activation and degranulation in response to a wide variety of agonists including endogenous neuropeptides such as substance P and cortistatin, microbial defense peptides, and eosinophil granulate proteins. MRGPRX2 and several of its agonists have been implicated in a range of diseases including chronic urticaria, atopic dermatitis and asthma. Our objective was to investigate the ability of the selective small molecule MRGPRX2 antagonist EP262 to inhibit mast cell activation and degranulation in vitro as well as in vivo in MRGPRX2 Knockin (KI) mice.

Methods: Antagonist pharmacology was characterized in vitro in MRGPRX2-overexpressing stable cell lines, LAD2 mast cells and peripheral stem cell-derived mast cells (PSCMCs) utilizing multiple signaling pathways. Functional human MRGPRX2 KI mice and Mrgprb2 Knockout (KO) mice were generated to test the ability of orally dosed EP262 and of Mrgprb2 KO to inhibit mast cell degranulation in vivo using the passive cutaneous anaphylaxis assay.

Results: EP262 potently inhibited MRGPRX2 activation and degranulation of mast cells induced by a wide variety of MRGPRX2 agonists, functioning as an inverse agonist. EP262 also blocked the release of tryptase and inflammatory cytokines in human mast cells. Orally administered EP262 inhibited mast cell degranulation and vascular permeability in response to MRGPRX2 agonists in MRGPRX2 KI mice with high in vivo potency; effects that were replicated in Mrgprb2 KO mice. EP262 demonstrated excellent ADME/PK properties supportive of once-a-day oral dosing.

Conclusion: EP262 is a potent MRGPRX2 antagonist with favorable pharmaceutical properties that inhibits mast cell degranulation, both in vitro and in vivo. and is being advanced as a clinical development candidate for the potential treatment of a broad range of mast cell mediated diseases.

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