EVO756: An Emerging Oral MRGPRX2 Blocker with Compelling Data from Early Studies

Jamie Harden[1], Sreya Bagchi[1], Stefan Frischbutter[2,3], Jorg Scheffel[2,3], Han Gao[2,3], Nana Shi[2,3], Alexandra Pavel[1], Claudia Montlollor-Abalate[1], Andrea Kim[1], Janice Drew[1], Polina Bukshpun[1], Kelsey Santisteban[1], Dan Burge[1], Sarbjit S. Saini[4], Jeegar Patel[1], Lorena Riol-Blanco[1]

[1]Evommune, Inc. Palo Alto, CA, USA ; [2]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany; [4]Johns Hopkins University, School of Medicine, Division of Allergy and Immunology

Abstract

Chronic inflammatory diseases often involve complex neurogenic and mast cell-related pathways, with the Mas-Related G-Protein Coupled Receptor X2 (MRGPRX2) playing a pivotal role. This receptor, highly expressed on mast cells and peripheral neurons, has drawn attention for its involvement in non-IgE-driven mast cell degranulation and neurogenic inflammation, contributing to symptoms like itching, coughing, and pain. Because MRGPRX2 responds to a wide range of ligands in inflamed tissues, it is a promising target for therapeutics addressing conditions like chronic urticaria, atopic dermatitis, and severe asthma.

EVO756, a novel small molecule, has emerged as a promising oral inhibitor of MRGPRX2. Preclinical data demonstrate robust inhibition of MRGPRX2-mediated responses across experimental models, such as LAD2 cells, human skin-derived mast cells, and skin explants. These findings highlight its broad activity in targeting this receptor.

Initial human trials support EVO756's potential. A Phase 1 randomized, double-blind study showed it to be well-tolerated with a generally dose-proportional pharmacokinetic profile. Its mechanism of action was confirmed through a skin wheal challenge with icatibant, where significant reductions in wheal size affirmed effective receptor blockade.

EVO756 stands out as an innovative therapy with the potential to regulate MRGPRX2-mediated processes. Its favorable early-stage results pave the way for further investigations into its clinical utility for managing mast cell-driven and neuro-inflammatory diseases.

Background

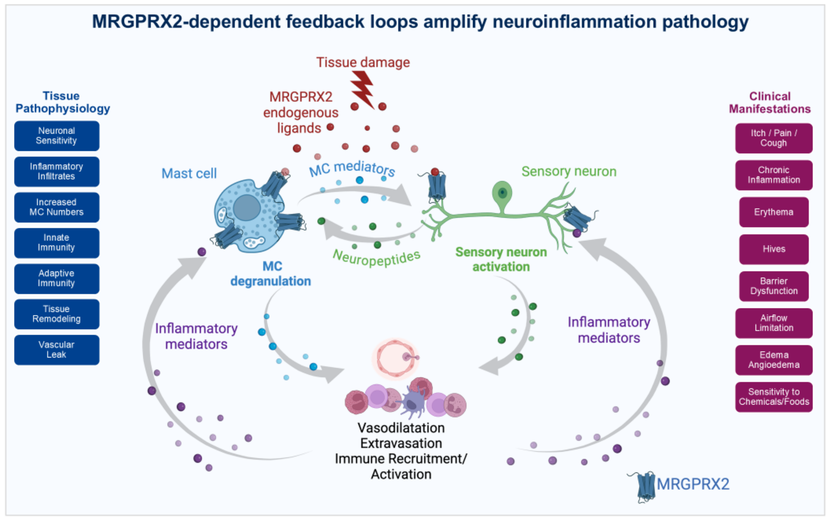


Figure 1. Pivotal Role of MRGPRX2 in Mast Cell Activation and Neuroinflammation

EVO756 Prevents Mast Cell Degranulation *In Vitro*

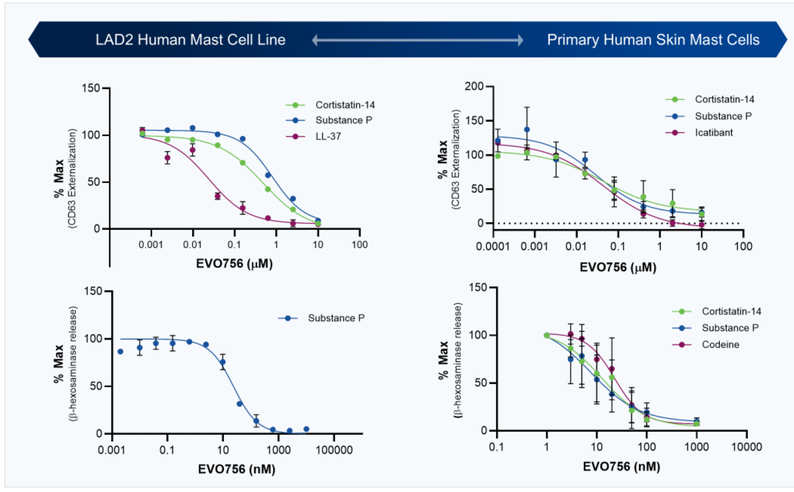


Figure 3. Inhibition of MRGPRX2-mediated mast cell degranulation by EVO756. LAD2 and primary human skin mast cells were treated with EVO756 at varying concentrations for 5 minutes. Cells were then incubated with MRGPRX2 agonists at greater than EC80 concentrations. For assays assessing CD63 surface expression, cells were incubated for 1 hour with agonists before flow cytometry-based analysis of CD63 expression was performed. For the β-hexosaminidase assay, released versus cellular content of the enzyme was detected in the supernatant and cell pellets after 1 hour of incubation with agonists.

Icatibant is a prototypical MRGPRX2 ligand and is inhibited by EVO756

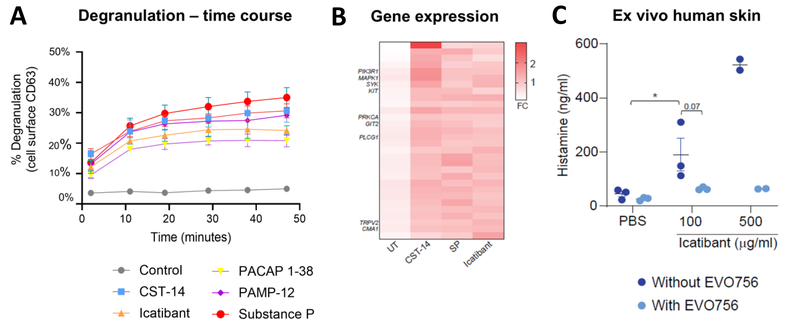
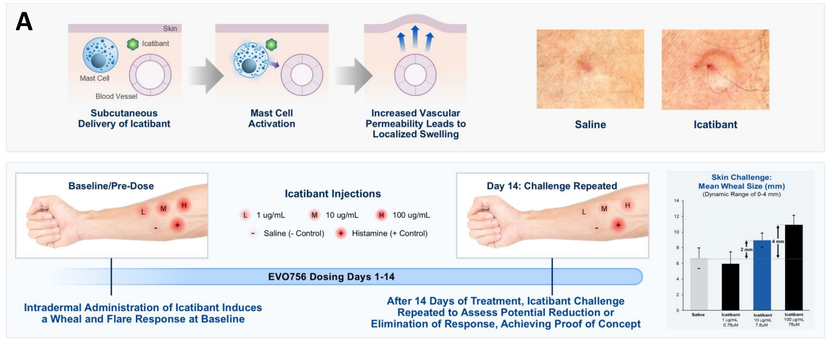


Figure 4. Response of icatibant compared to other MRGPRX2 agonists and inhibition by EVO756 is an *ex vivo* skin assay (A) Time-course of phsMC degranulation upon stimulation with MRGPRX2 agonists, as determined by the percent of phsMCs with cell-surface CD63 staining (B) Common differentially expressed genes in phsMCs stimulated with MRGPRX2 agonists versus untreated cells (C) Histamine concentrations in dISF collected from ex vivo human skin experiments. EVO756 (EVO) was injected prior to injection at the same site with icatibant. Hollow microneedles were utilized to extract dISF from the injection sites from which histamine levels were quantified.

Multiple Ascending Dose (MAD) Safety Summary	Placebo (Pooled)	Cohort B1 10 mg BID	Cohort B2 30 mg BID	Cohort B3 100 mg BID	Cohort B4 240 mg BID	Cohort B5 500 mg QD
n	19	11	12	12	11	12
Total Number of TEAEs	13	8	4	14	10	10
Total Number of Subjects Who Had at Least 1 TEAE	8 (42.1%)	4 (36.4%)	4 (33.3%)	5 (41.7%)	2 (18.2%)	5 (41.7%)
AEs in More than 1 Subject:						
Headache	1 (5.3%)	0	1 (8.3%)	1 (8.3%)	1 (9.1%)	4 (33.3%)
Dizziness	0	1 (9.1%)	0	0	1 (9.1%)	0
Somnolence	0	0	0	2 (16.7%)	0	0
Catheter Site Pain	1 (5.3%)	0	1 (8.3%)	1 (8.3%)	0	0
Catheter Site Bruise	1 (5.3%)	1 (9.1%)	0	0	0	0
Alopecia	1 (5.3%)	0	0	1 (8.3%)	0	0
Skin Irritation	1 (5.3%)	1 (9.1%)	0	0	0	0
Sore Throat	1 (5.3%)	0	0	0	0	1 (8.3%)

Skin Challenge Test: Proof of Concept and Target Engagement for Chronic Urticaria



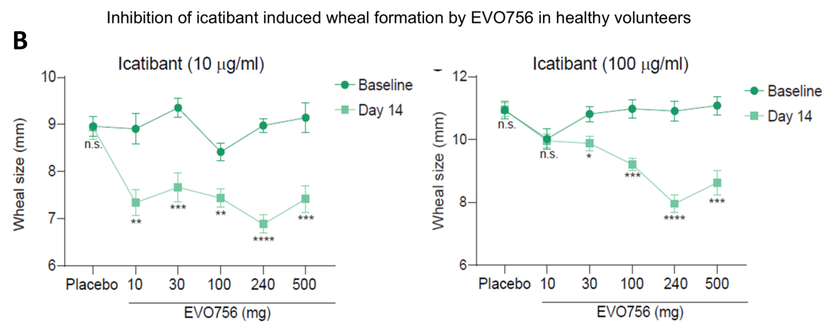


Figure 5. Icatibant skin challenge study design and results (A). Phase 1 healthy volunteer skin challenge study design with oral EVO756. In brief, the wheal response in healthy volunteers was determined at baseline in response to saline, histamine, or 1, 10, and 100ug/mL of an intradermal injection of icatibant. Healthy volunteers were given placebo, 10, 30, 100, 240 mg of EVO756 BID or 500 mg QD for 14 days. After 14 days of oral EVO756, the skin challenge was repeated as performed at baseline, and reduction in wheal size was noted. Average wheal sizes noted in this study shown in lower right (B) Dose-dependent inhibition of icatibant-induced wheal size in healthy volunteers.

EVO756 broadly inhibits MRGPRX2 activation by all ligands tested

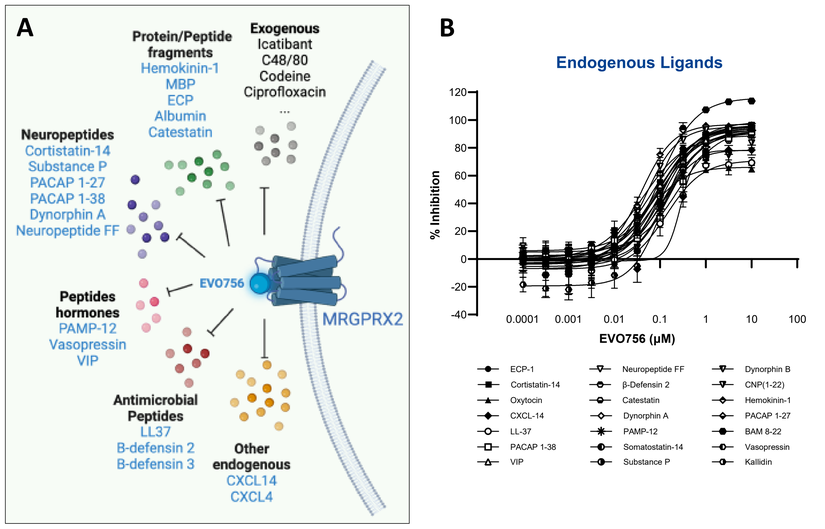
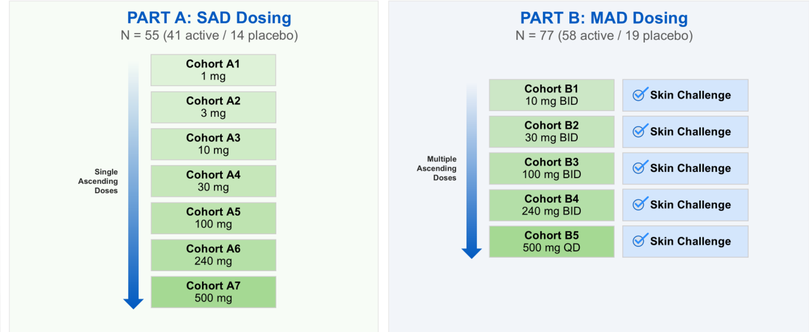


Figure 2. MRGPRX2 ligands and concentration dependent inhibition of MRGPRX2 signaling by EVO756 in CHO-MRGPRX2 transfectant. (A) Ligands that activate MRGPRX2 (B) CHO cells expressing MRGPRX2 were loaded with the FLIPR calcium dye and incubated for 30 min with EVO756 at varying doses. Subsequently, various endogenous and exogenous (*not shown*) agonists were added by the FLIPR Penta instrument and calcium flux measured over time. Percent inhibition was calculated based on CHO-MRGPRX2 cells treated with only EVO756 or only agonist.

EVO756: Proof of Concept Study Design



Single Ascending Dose (SAD) Safety Summary	Placebo (Pooled)	Cohort A1 1 mg	Cohort A2 3 mg	Cohort A3 10 mg	Cohort A4 30 mg	Cohort A5 100 mg	Cohort A6 240 mg	Cohort A7 500 mg
n	14	6	6	5	6	6	6	6
Total Number of TEAEs	8	2	1	2	3	3	3	3
Total Number of Subjects Who Had at Least 1 TEAE	6 (42.9%)	2 (33.3%)	1 (16.7%)	2 (40.0%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	2 (33.3%)
Events in More than 1 Subject								
Headache	3 (21.4%)	2 (33.3%)	0	0	1 (16.7%)	1 (16.7%)	0	2 (33.3%)
Dizziness	1 (7.1%)	0	0	0	0	0	1 (16.7%)	0
Catheter Site Pain	0	0	0	0	1 (16.7%)	1 (16.7%)	0	0
Diarrhea	1 (7.1%)	0	0	0	0	1 (16.7%)	0	0
Lymphadenopathy	0	0	0	2 (40.0%)	0	0	0	0

Conclusions

- EVO756 is a novel, oral, small molecule inhibitor of MRGPRX2
- EVO756 inhibits MRGPRX2 activation by multiple ligands in several *in vitro* assays
- EVO756 was evaluated in a Phase 1 Healthy Volunteer Study, which included an icatibant skin challenge component
- EVO756 inhibited icatibant-induced wheals in a dose-dependent manner
- EVO756 is a potential therapeutic for the treatment of diseases caused by overactivation of mast cells and neuroinflammation mediated by MRGPRX2, such as chronic urticarias and atopic dermatitis

Acknowledgements and Disclosures

Illustrations were created with BioRender.com. JLH, SB, CMA, AP, JL, AK, JD, PB, KS, DB, JP, and LRB are employees of, and hold stock in, Evommune.