Results from a Phase 1 Study

EVO756, an oral MRGPRX2 antagonist, is well-tolerated and demonstrates target engagement

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Conflict of Interest Disclosure

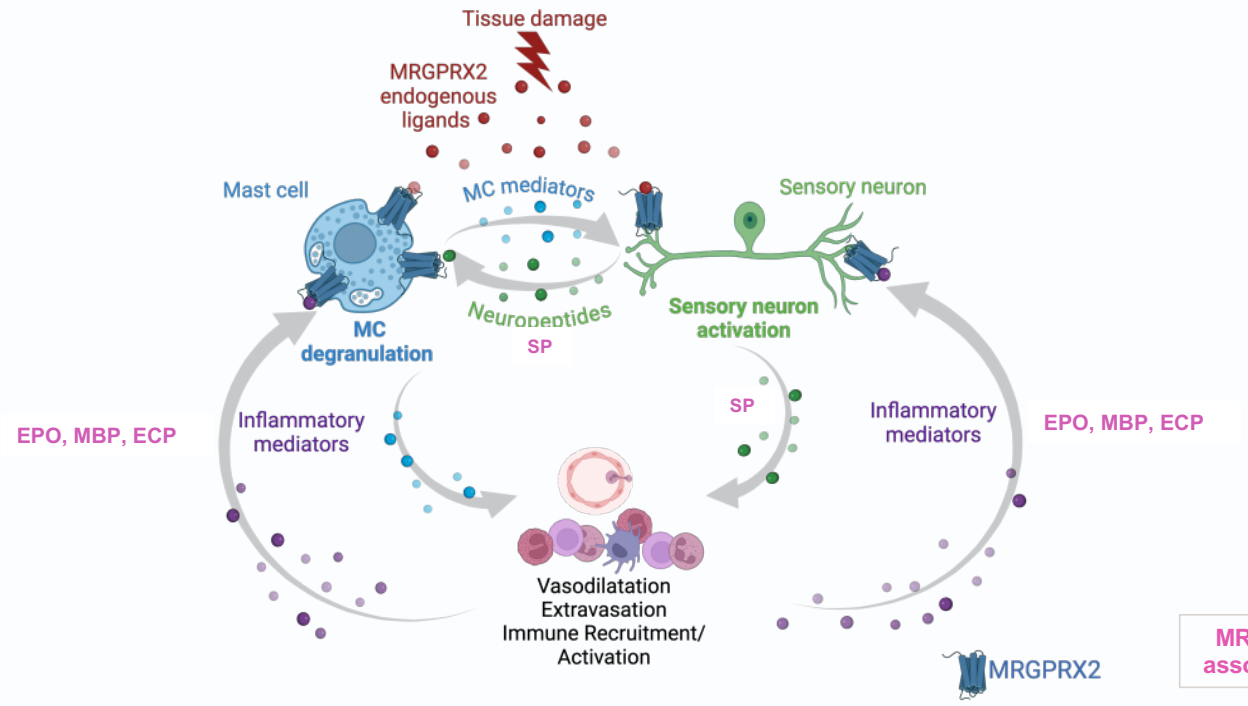
- I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	NIH, Novartis, Escient, Allakos, Jasper
Receipt of honoraria or consultation fees:	Allakos, Granular Therapeutics, Genetech, Celldex, Evommune, Novartis, Escient, Celltrion, Sanofi, Nucor, GSK
Participation in a company sponsored speaker's bureau:	None
Stock shareholder:	None
Other support (please specify):	Editor Up to Date

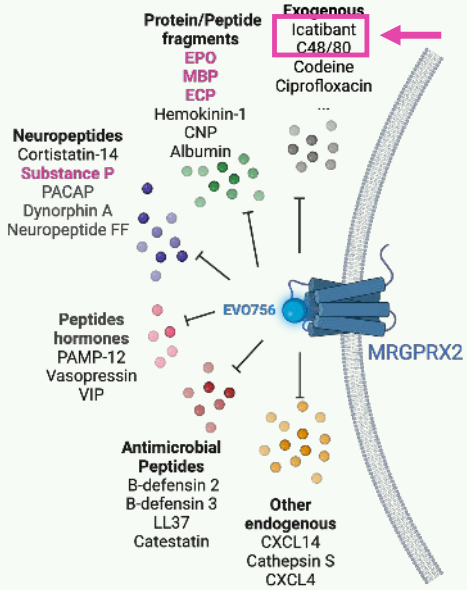
MRGPRX2-dependent Mast Cell-Neuron interactions regulate multiple feedback mechanisms driving pathophysiological processes in CSU

Targeting MRGPRX2 may improve CSU signs and symptoms

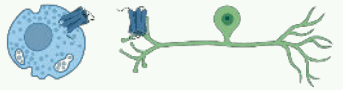
MRGPRX2-dependent feedback loops amplify neuroinflammation pathology



MRGPRX2: Nexus for MC/neuron activation by multiple disease relevant ligands



MRGPRX2 Ligands associated with CSU



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MRGPRX2's Potential Role in CSU

Long recognized 48/80 skin reactivity increased in CSU patients

Bedard *JACI* 1986
Brunet *JACI* 1990

MRGPRX2 identified as receptor on skin MCs for 48/80 and other ligands

McNeil *Nature* 2014

Increased X2 expression noted in skin biopsies of CSU subjects

Fujisawa *JACI* 2014

Increased skin reactivity with X2 ligand testing (icatibant)

Shtessel *JID* 2020

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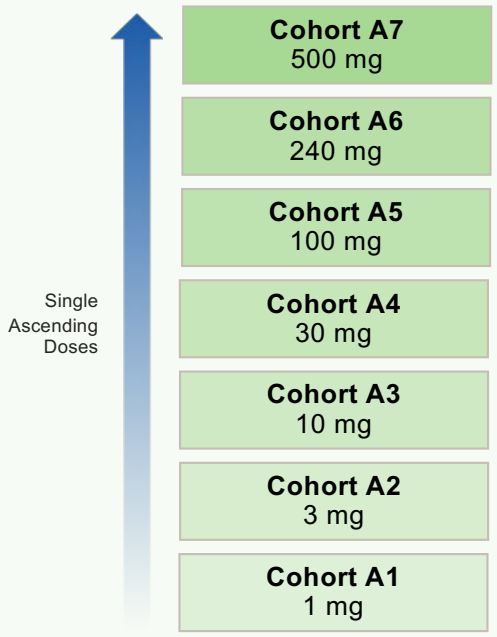
EVO756 is an Oral MRGPRX2 Antagonist Targeted for CSU

Phase 1 Study Design: Single and Multiple Ascending Dose Cohorts with EVO756

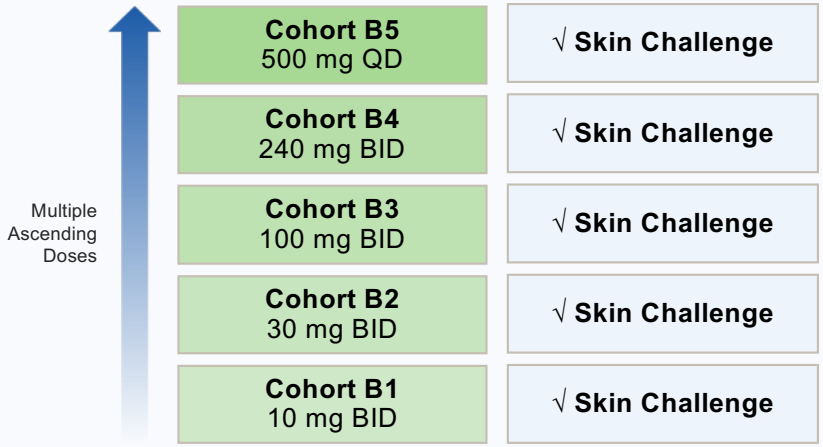
PART A: SAD Dosing

N= 55 (41 active/14 placebo)



PART B: MAD Dosing

N=77 (58 active/19 placebo)



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Safety – Single Ascending Dose Cohorts

	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 One TEAE	6 (42.9%)	2 (33.3%)	1 (16.7%)	2 (40%)	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
Lymphadenpathy	0	0	0	2 (40%)	0	0	0	0

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Safety – Multiple Ascending Dose Cohorts (14 days)

	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 One TEAE	8 (42.1%)	4 (36.4%)	4 (33.3%)	5 (41.7%)	2 (18.2%)	5 (41.7%)
AEs in More than One 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%)

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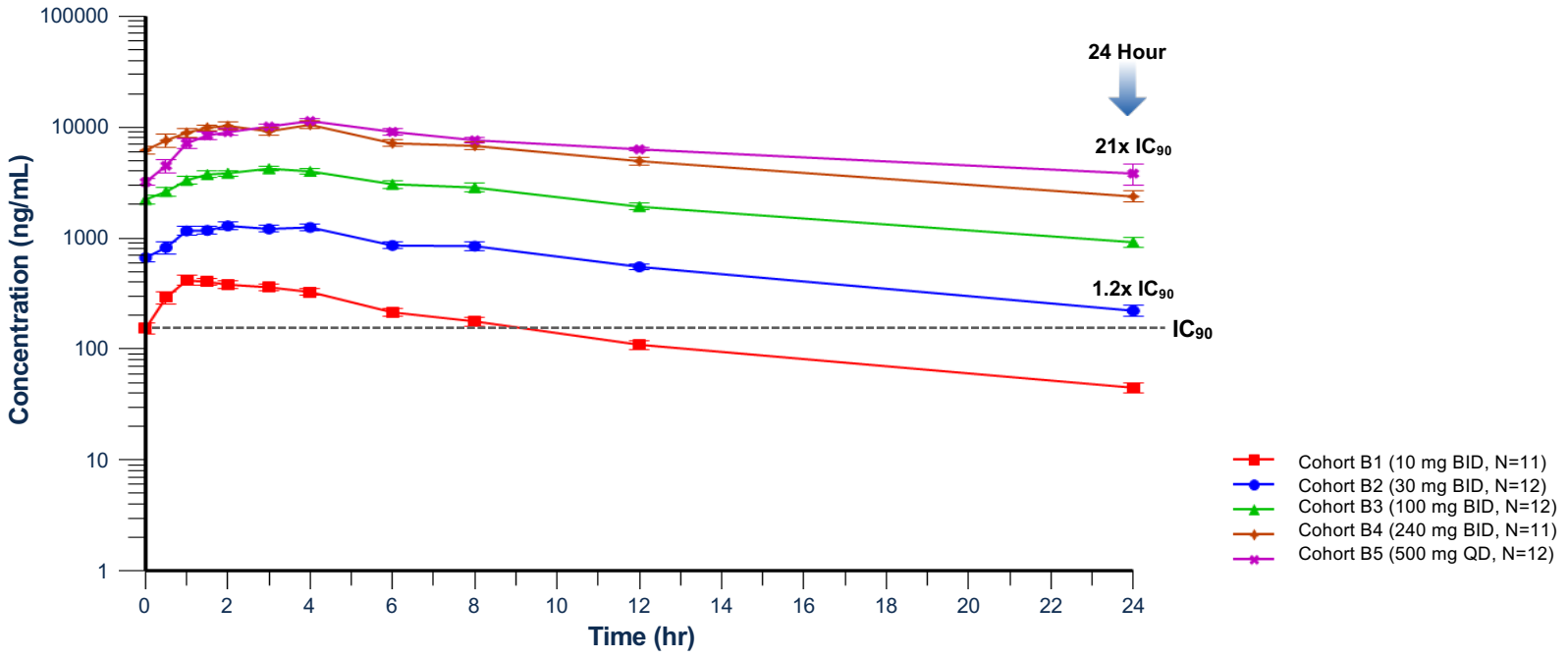
Multiple Dose Pharmacokinetics (14 Days)

Half-life of 8-12 hours supports once and twice daily dosing regimens

Log-Linear Plots of Mean EVO756 Plasma Concentrations vs Time



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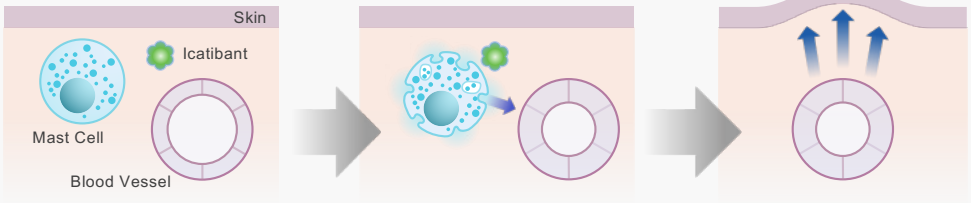
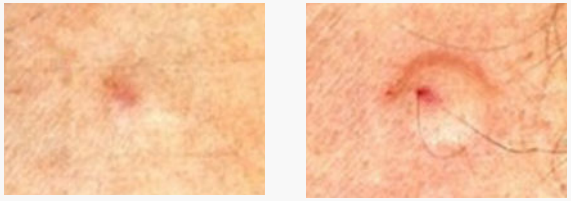
Proof of Concept & Target Engagement for Chronic Urticaria



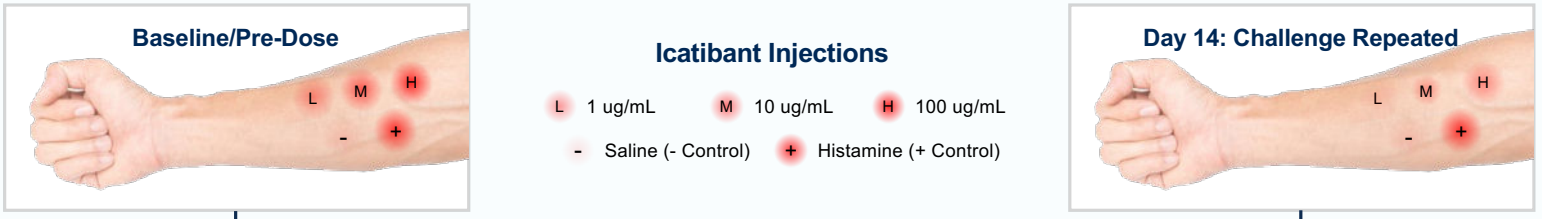
Subcutaneous Delivery of Icatibant

Mast Cell Activation

Increased Vascular Permeability Leads to Localized Swelling



Saline **Icatibant**



Intradermal Administration of Icatibant Induces a Wheal and Flare Response at Baseline

After 14 Days of Treatment, Icatibant Challenge Repeated to Assess Potential Reduction or Elimination of Response, Achieving Proof of Concept

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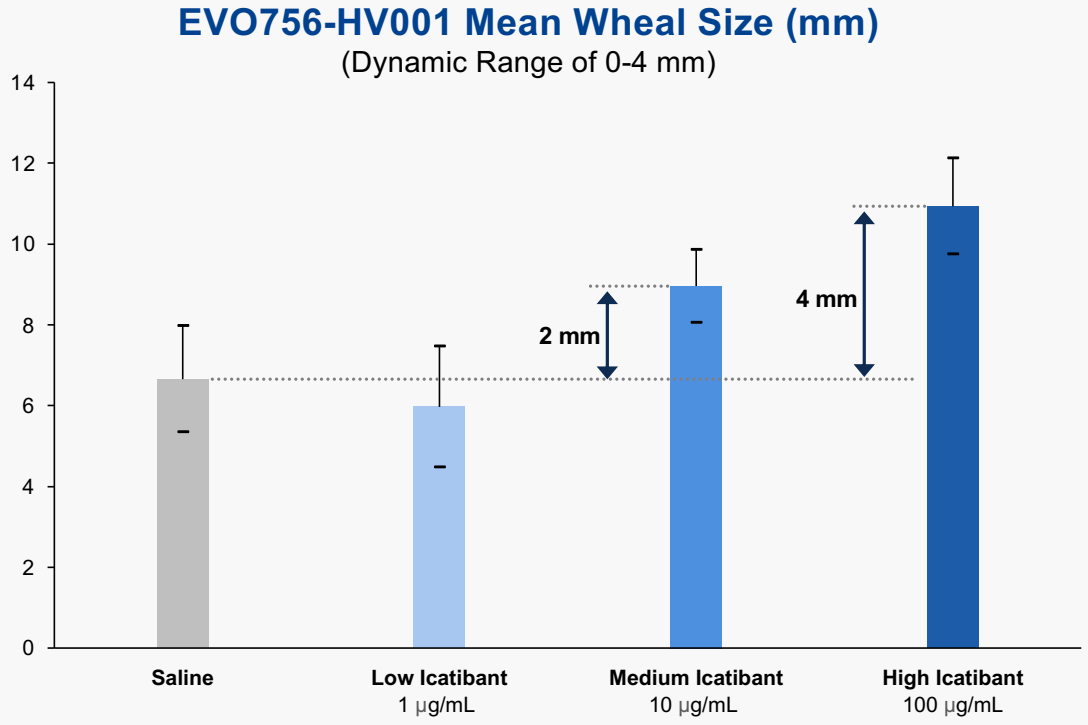
Icatibant Skin Challenge Assesses EVO756 Target Engagement

- ***In vitro*** **pharmacology of Icatibant is comparable to that of all MRGPRX2 ligands tested**
- **Highly consistent and reproducible wheals formed with Icatibant at 10 and 100 µg/mL and with histamine control**



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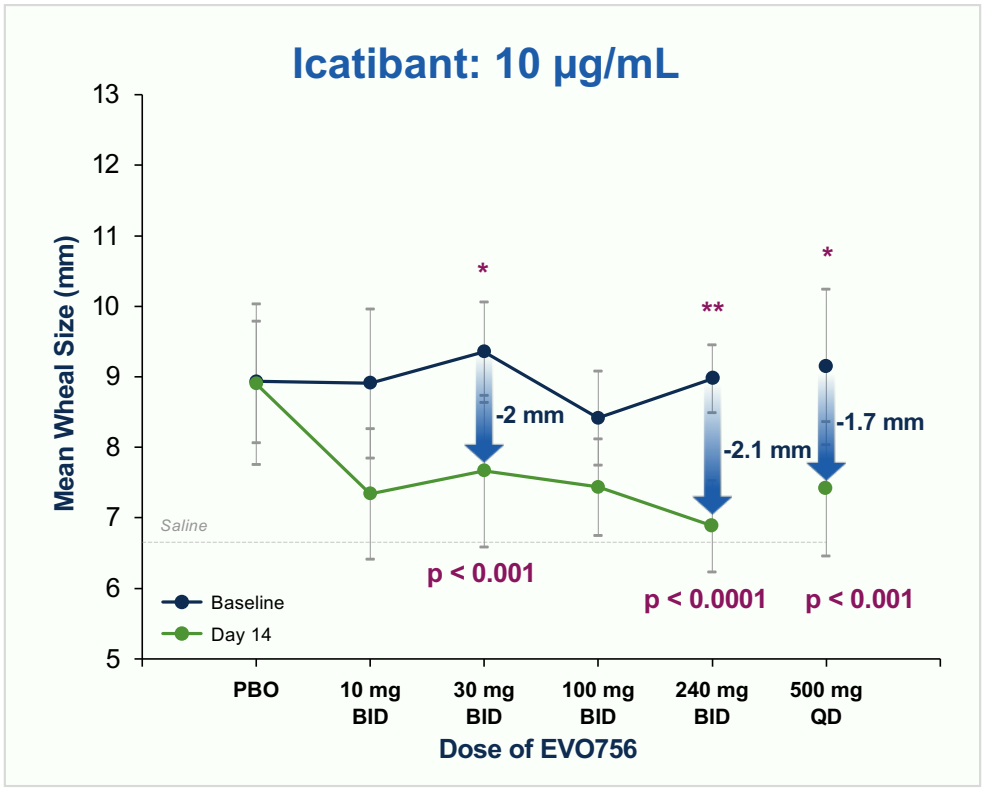
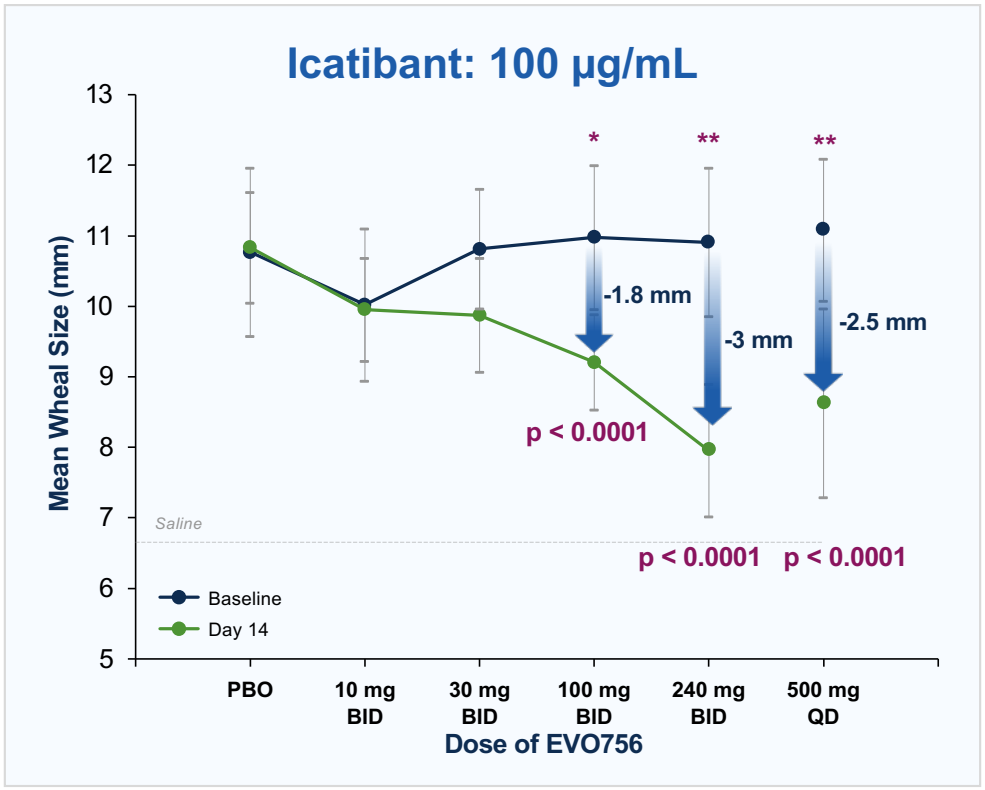
EVO756 Robustly Decreases Icatibant Wheal Size in a Dose-Dependent Manner





Error bars represent standard deviation; *p < 0.001; **p < 0.0001; p-value from LS-means change from baseline in wheal size in a Mixed Model Repeated Measures (MMRM) analysis. Bonferroni adjustment made for multiple comparisons – only comparisons which reached statistical significance of p<0.001 are noted.

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EVO756 Phase 1 Data Support Advancement to Phase 2

- EVO756 is well tolerated across all doses
- Pharmacokinetics support once and twice daily dosing
- Clear target engagement
- Further evaluation in patients with active CSU and CIndU is warranted

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