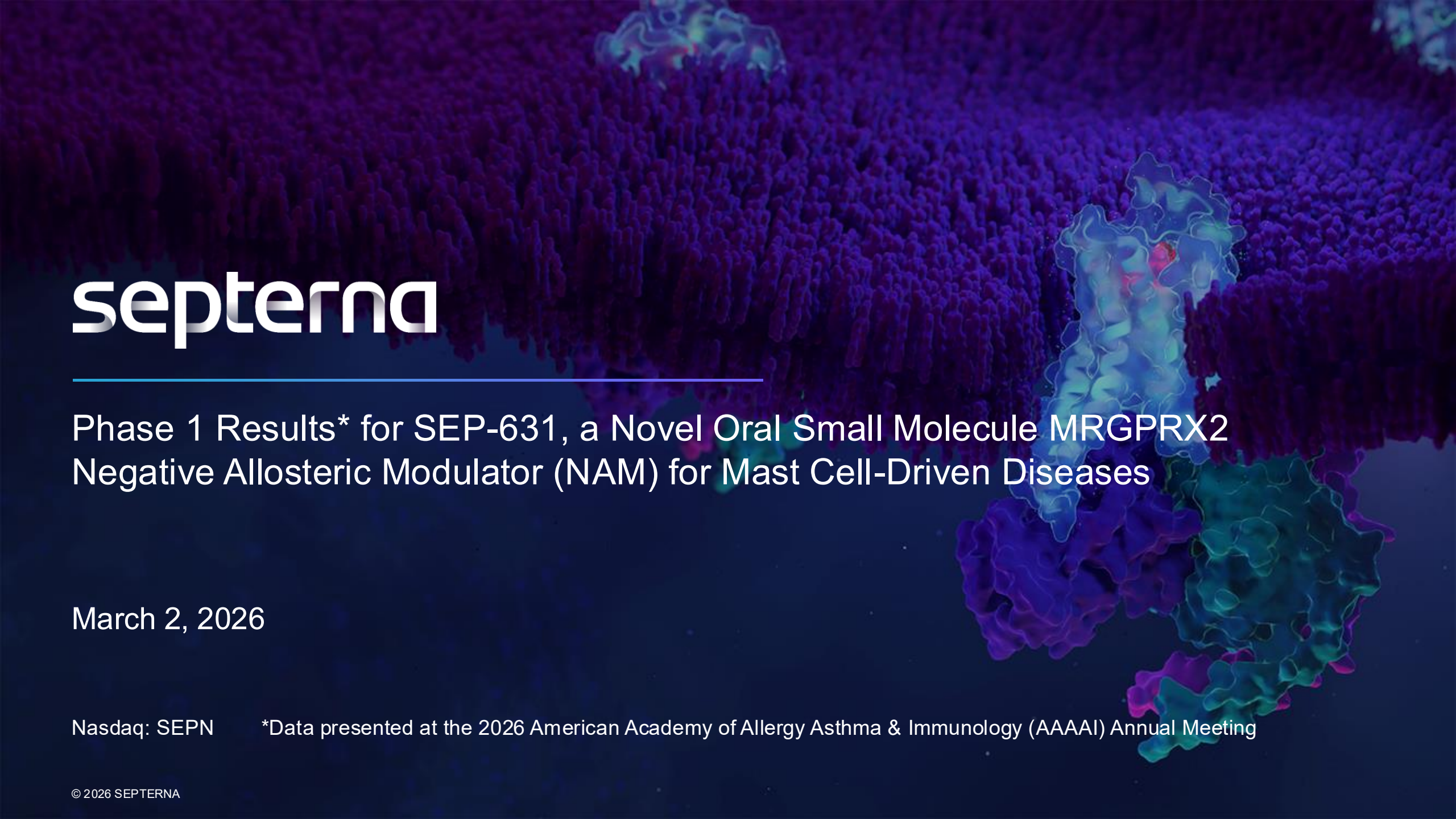

Phase 1 Results* for SEP-631, a Novel Oral Small Molecule MRGPRX2 Negative Allosteric Modulator (NAM) for Mast Cell-Driven Diseases

March 2, 2026

Nasdaq: SEPN

*Data presented at the 2026 American Academy of Allergy Asthma & Immunology (AAAAI) Annual Meeting

Forward-Looking Statements

This presentation contains express or implied forward-looking statements of Septerna, Inc. (the "Company," "we," or "our") within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. All statements other than statements of historical facts contained in this presentation, including statements regarding our business strategy, plans, estimated R&D program milestones and objectives of management are forward-looking statements. Such forward-looking statements include, but are not limited to, statements regarding: the continued advancement of our PTH1R agonist program, including the planned initiation of a Phase 1 clinical trial for SEP-479 in the first half of 2026 subject to successful completion of regulatory submissions; the continued advancement of SEP-631, including the plan to initiate a Phase 2b clinical study in CSU in the second half of 2026 subject to the successful completion of long-term preclinical toxicology studies; the role of MRGPRX2 in mast cell-driven diseases; the timing, progress and results of conducting our research and development programs, including our plans to advance the TSHR program; the intended and potential benefits of the collaboration with Novo Nordisk, including our ability to jointly discover, develop and commercialize multiple potential oral small molecule therapies for obesity, type 2 diabetes, and other cardiometabolic diseases and the potential resulting milestones and royalties (if any); our ability to demonstrate, and the timing of, preclinical proof-of-concept *in vivo* and *ex vivo* for multiple programs; the potential of our proprietary Native Complex Platform®; the ability of preclinical or Phase 1 safety and efficacy observations to successfully translate into clinical outcomes; the size and growth potential of the markets for our current and future product candidates; our expectations regarding strategic plans for our business, product candidates, and technology; the scope of protection we are able to establish and maintain for intellectual property rights covering our Native Complex Platform® and our product candidates; our ability to maintain existing collaborations and to identify and enter into future license agreements and collaborations; and the accuracy of our estimates regarding expenses and capital requirements, including our expected cash runway at least into 2029. Such forward-looking statements reflect the current views of the Company and are subject to known and unknown risks and other factors, which are, in some cases, beyond the Company's control. Risks that contribute to the uncertain nature of the forward-looking statements include those risks and uncertainties set forth in the section titled "Risk Factors" in our most recent Annual Report on Form 10-K for the year ended December 31, 2024, as well as any subsequent filings with the Securities and Exchange Commission.

Certain information in this presentation (including market data and statistical information) and statements made orally during this presentation are the good faith estimates of management and have been obtained from various sources (including third-party sources such as independent industry publications, governmental publications, and reports by market research firms), and we do not guarantee the accuracy or completeness of such information.

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Agenda

- **Septerna: Building a World-Class GPCR-Focused Biotechnology Company**
- **SEP-631: Oral Small Molecule MRGPRX2 Negative Allosteric Modulator (NAM)**
- **SEP-631: Phase 1 Healthy Subject Trial Results**
  - Safety, Pharmacokinetics, and Pharmacodynamics (with Icatibant Skin Challenge)
- **SEP-631: Broad Opportunity in Mast-Cell Driven Diseases**
- **Question & Answer Session**

Jeff Finer, MD, PhD
CEO

Liz Bhatt, MS, MBA
President & COO

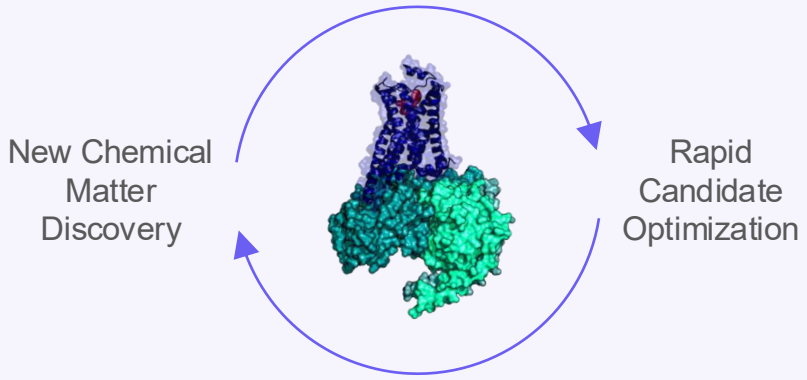
Jae Kim, MD
CMO

Gil Labrucherie, CFA, JD
CFO

Septerna: Pioneering a New Era of GPCR Drug Discovery with Oral Small Molecules

- **GPCR drug discovery has been concentrated to a small number of targets - our strategy is to unlock difficult-to-drug GPCRs**

- **Our Native Complex Platform®** enables us to rapidly discover and optimize small molecules using iterative structure-based drug design



- **Growing portfolio of clinical programs** focused on validated targets, early clinical readouts, and large commercial opportunities
- **SEP-631 is a MRGPRX2 NAM** with the potential to be a pipeline-in-a-product for mast cell-driven diseases
- **SEP-479 is a PTH1R agonist** that has the potential to be the first oral PTH replacement therapy for hypoparathyroidism patients

- **Well-capitalized with cash runway to drive research and development pipelines at least into 2029**

Advancing a Deep Portfolio of Oral Small Molecule GPCR-Targeted Programs

Wholly-Owned Programs		Development Status			
Program / Target Mode of Action	Therapeutic Area Indications / US Patient Population	Discovery	IND-enabling	Phase 1	Phase 2
SEP-479 (PTH1R) Agonist	Endocrinology Hypoparathyroidism: ~70k			Phase 1 initiation* anticipated in 1H 2026	Anticipate Phase 1 topline data in late 2026 / early 2027
SEP-631 (MRGPRX2) Negative Allosteric Modulator	Immunology and Inflammation CSU: ~1.5mm Other mast cell diseases				Phase 2 initiation* anticipated in 2H 2026
TSHR Program Negative Allosteric Modulator	Endocrinology Graves' disease: ~2mm Thyroid eye disease: ~1mm				
Research Areas: Neurology, Women's Health, Cardiovascular Disease and Respiratory Disease					

Partnered Programs		Partner
Metabolic Programs GLP-1R, GIPR, GCGR + Undisclosed	Obesity and Other Cardiometabolic Diseases	novo nordisk®
Undisclosed	Undisclosed	VERTEX

* Pending successful completion of regulatory submissions

SEP-631: Oral Small Molecule MRGPRX2 NAM

Targeting MRGPRX2 for Mast Cell-Driven Diseases

MRGPRX2 is a Key Regulator of Mast Cell Degranulation Activated by Several Endogenous Ligands

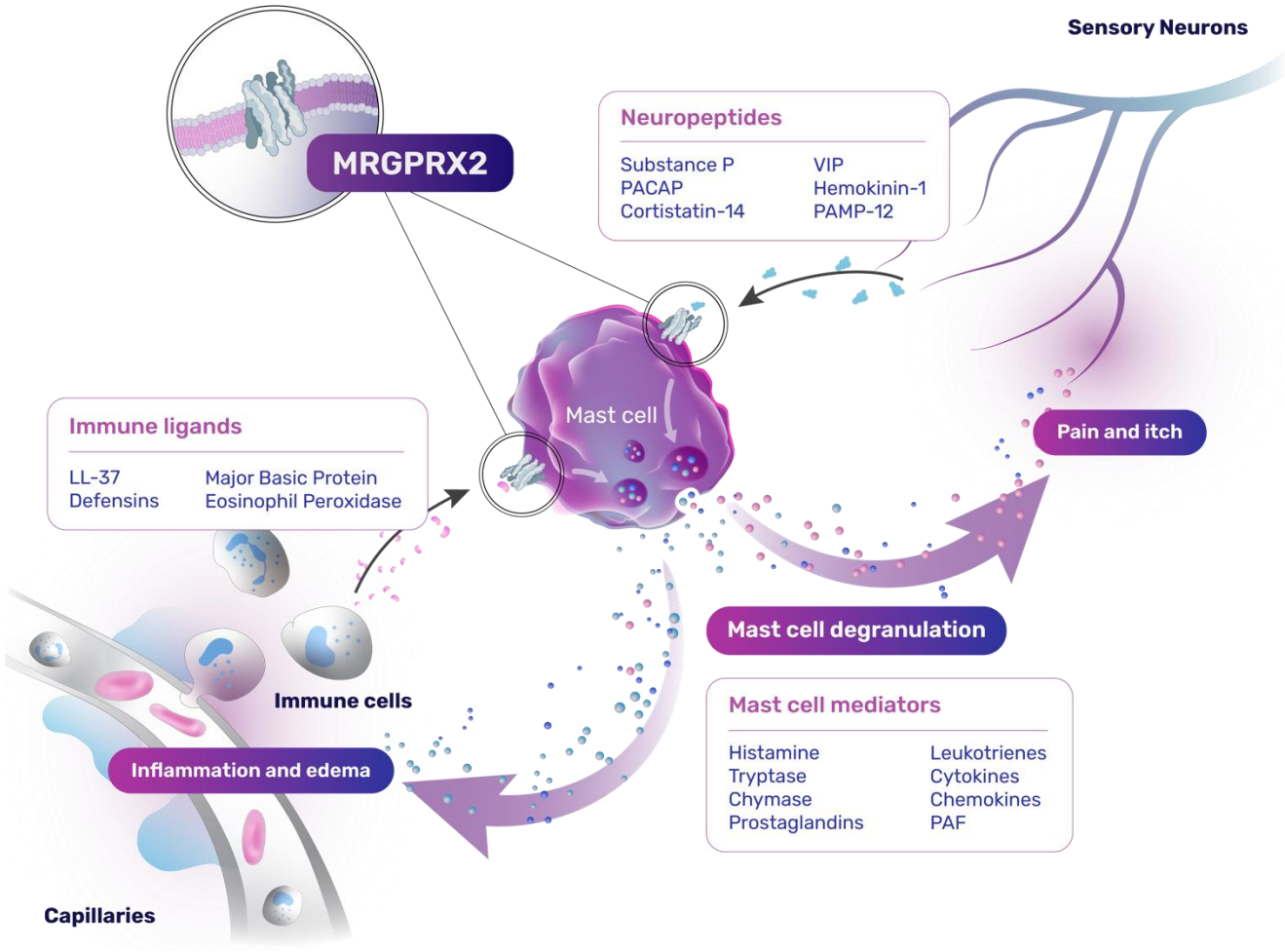
MRGPRX2 is activated by a host of endogenous agonists leading to IgE-independent mast cell degranulation

- Include several neuropeptides and immune ligands

Mast cell degranulation leads to release of mediators which cause pain, itch, inflammation, and edema

- Pain and itch are driven by mast cells co-localized with sensory neurons
- Inflammation and edema are driven by mast cell mediator effects on tissue capillaries leading to vasodilation, vascular permeability, and leukocyte recruitment

Targeting MRGPRX2 has the potential to disrupt feedback loops that drive these effects



Broad Opportunity for New Medicines Targeting Several Mast Cell-Driven Diseases

Mast cells are key mediators of allergic and inflammatory diseases

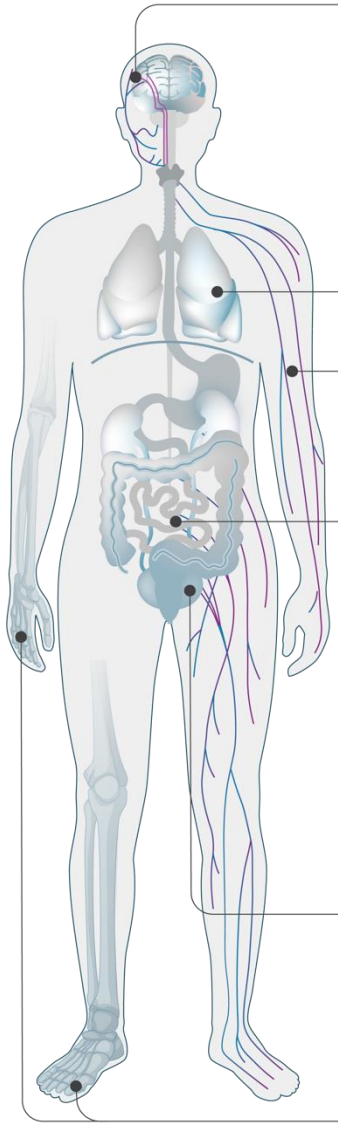
- Reside in organ systems throughout the body

Degranulation results in the release of an array of mediators which result in pain, itch, and inflammation

- Contributes to pathophysiology of several diseases

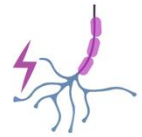
Targeting MRGPRX2, which leads to IgE-independent mast cell degranulation, has multi-indication potential

- Breadth of potential represents a pipeline-in-a-product opportunity



Neurology

Migraine

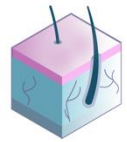


Allergy / Respiratory

Asthma
Food Allergy
Chronic Rhinosinusitis (CRS)

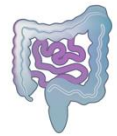
Skin

Chronic Spontaneous Urticaria (CSU)
Chronic Inducible Urticaria (CIndU)
Atopic Dermatitis (AD)
Prurigo Nodularis (PN)



Gastrointestinal

Irritable Bowel Syndrome (IBS)
Inflammatory Bowel Disease (IBD)



Urology / Gynecology

Interstitial Cystitis (IC)
Endometriosis

Rheumatology

Gout
Rheumatoid Arthritis (RA)

SEP-631: MRGPRX2 NAM with a Potentially Differentiated Profile for Mast Cell-Driven Diseases

SEP-631 is a negative allosteric modulator (NAM)

- Binds to a novel allosteric site, distinct from the agonist binding pocket

Potently inhibits MRGPRX2 activation with an insurmountable NAM profile

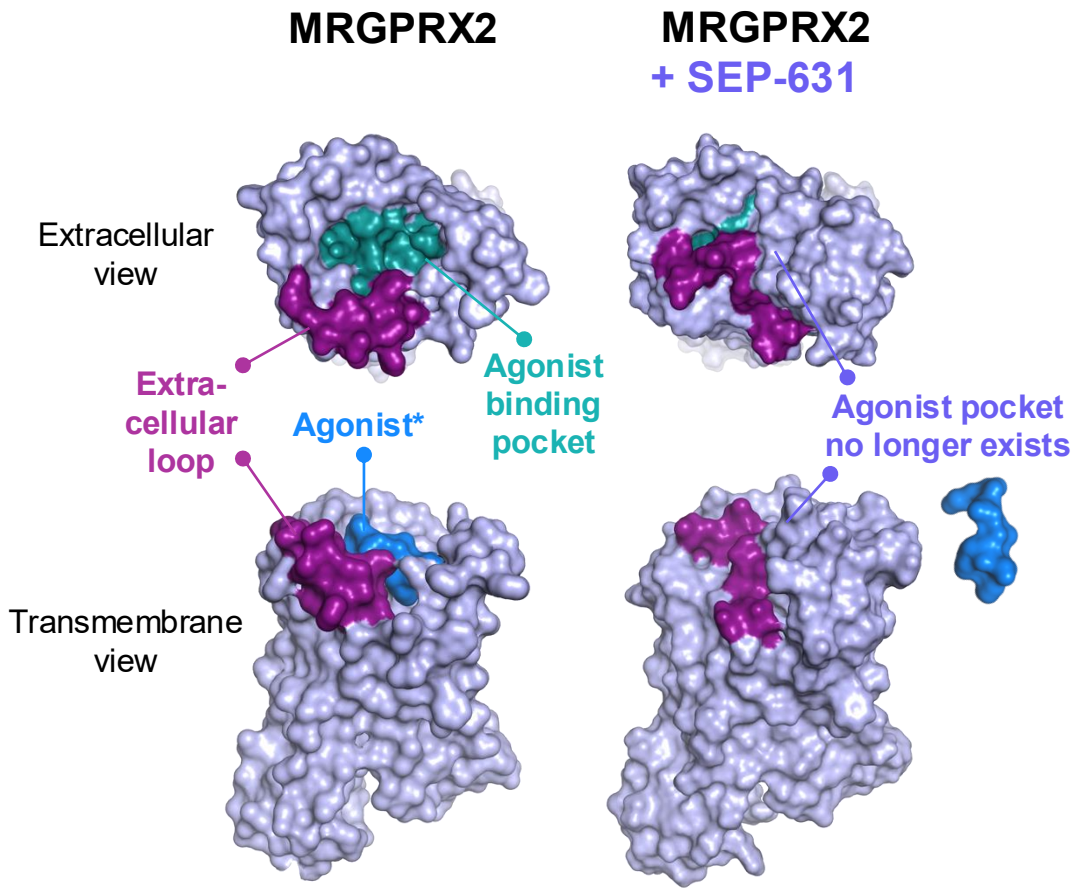
- Very high binding affinity (Ki ~0.5 nM)
- Slow dissociation rate ($t_{1/2}$ > 2 hours)

Locks MRGPRX2 in a state that prevents binding of all agonists, even at high agonist concentrations

- Potent inhibition of MRGPRX2-induced degranulation for both mast cell lines and primary human skin mast cells

PK profile across species projected to once-daily oral dosing in humans

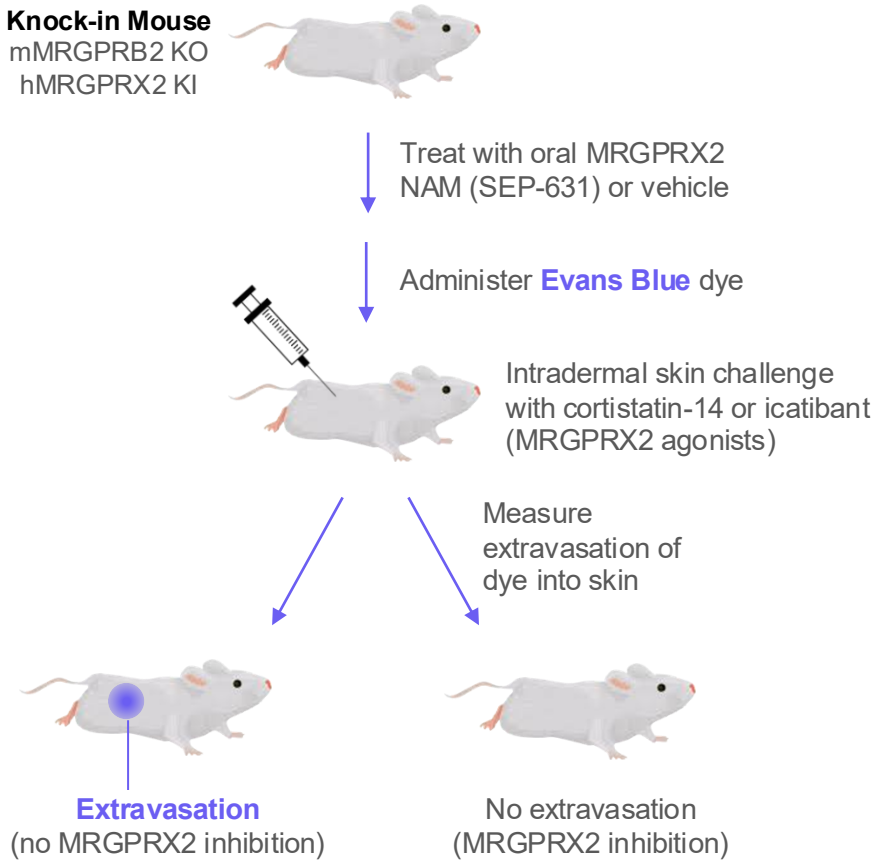
SEP-631 Induces a Structural Change in MRGPRX2 That Completely Closes the Agonist Binding Pocket



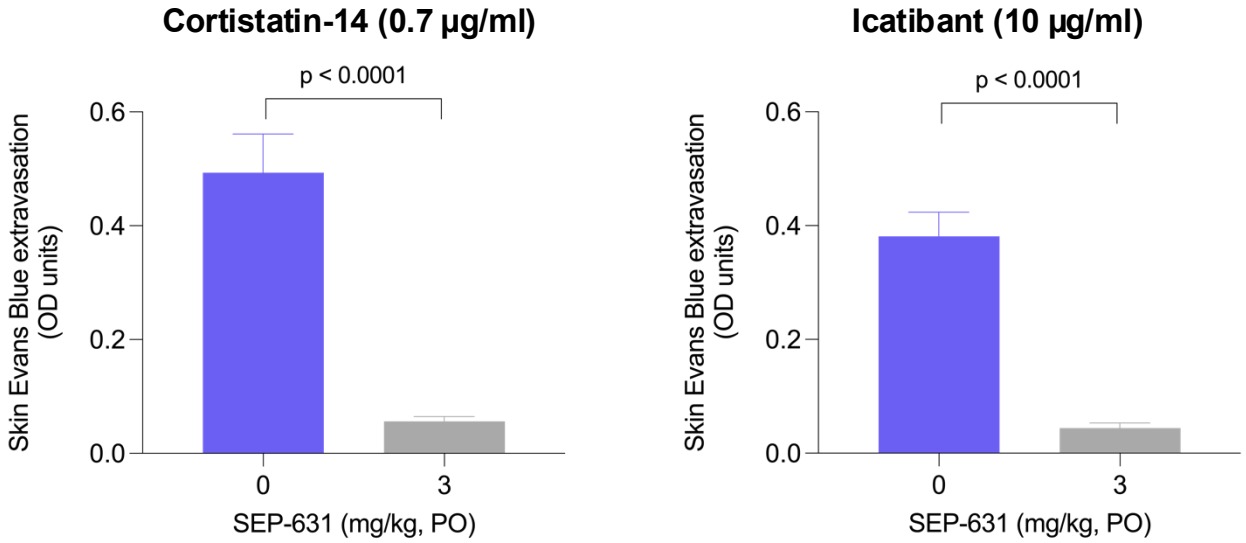
*Cortistatin-14

SEP-631 Inhibited MRGPRX2 Activation in Humanized Mouse Translational Model

Human MRGPRX2 Knock-in (KI) Mouse Model of Skin Extravasation



SEP-631 Potently Inhibited Skin Extravasation



SEP-631's insurmountable NAM profile translated to complete inhibition of MRGPRX2-mediated skin extravasation in a preclinical urticaria translational model

KO: gene knockout KI: gene knock-in

SEP-631 Preclinical Data Supports Potential Best-in-Class Profile

SEP-631 Preclinical Profile

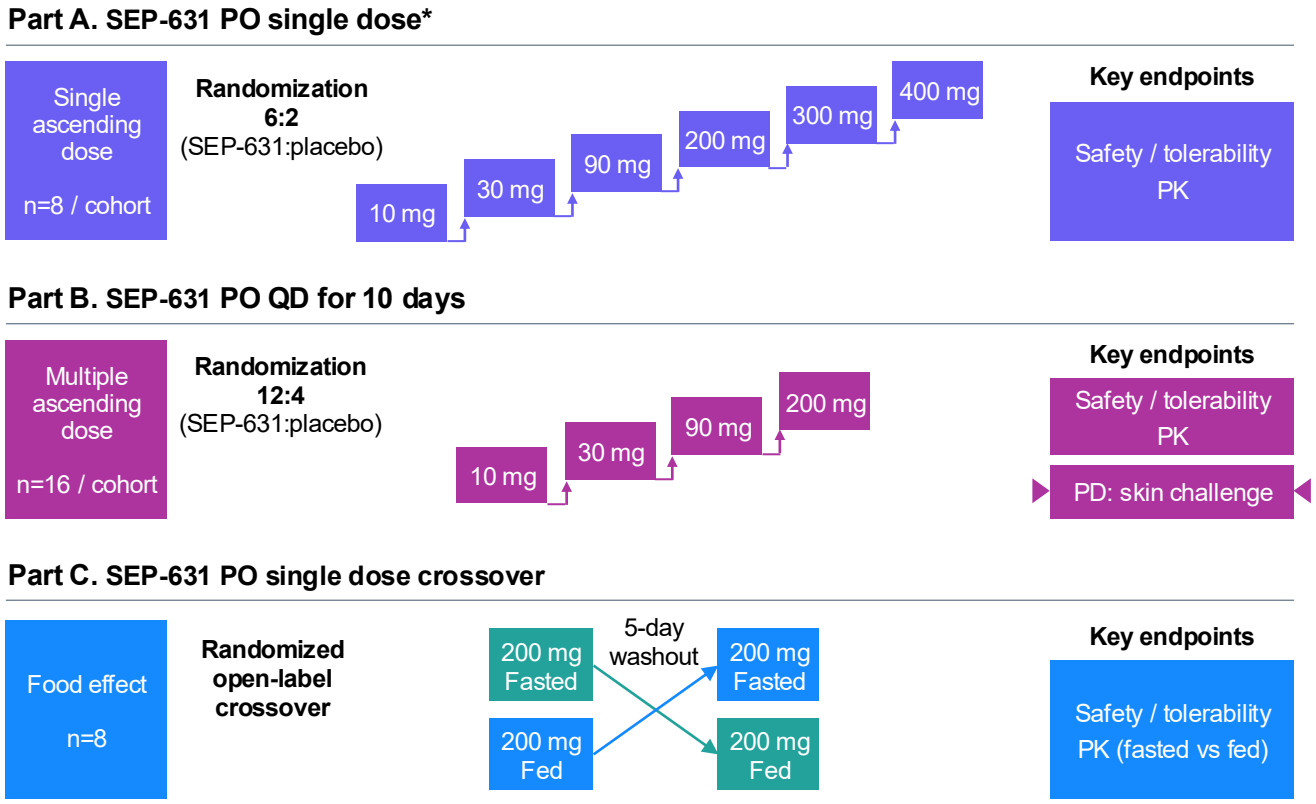
- **Subnanomolar binding affinity and slow off-rate kinetics**
- **Insurmountable negative allosteric modulator mechanism closes off agonist binding pocket**
  - Inability to activate receptor despite presence of high doses of endogenous agonists
- **Potent inhibition of MRGPRX2 activation in knock-in animals and primary human mast cells**
- **Excellent oral PK across species**
  - Projects to once-daily human dosing
- **Excellent pharmaceutical properties**
  - Low drug-drug interaction risk based on in vitro profiling
  - Low food effect risk based on preclinical studies
- **Generally well-tolerated in pharmacology and GLP toxicology studies**
- **Convenient tablet formulation developed**

First-in-Human, Proof-of-Mechanism Phase 1 Study of the Oral MRGPRX2 Antagonist SEP-631

SEP-631 Phase 1 Study Design

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Food Effects of SEP-631 in Healthy Adult Volunteers

- Part A: randomized, double-blind, placebo controlled, single ascending dose (SAD) study (n = 48)
- Part B: randomized, double-blind, placebo controlled, multiple ascending dose (MAD) study (n = 64)
- Part C: randomized, open-label, 2 period, crossover food effect study (n = 8)



*Sentinel dosing was used in SAD cohorts. Decisions for dose escalation and progression from single to multiple doses and food effect dosing were made by a Safety Review Committee

Safety: Single Dose Adverse Event Profile Comparable to Placebo

- **Rate of TEAEs with SEP-631 was comparable with placebo**
- **No severe or serious events were reported**
- **2 AEs of mild transaminase elevations (<1.5x ULN) observed with SEP-631 were not related to dose, and at rates comparable to placebo**

	Pooled placebo (n=12)	SEP-631 Single Dose						
		10 mg (n=6)	30 mg (n=6)	90 mg (n=6)	200 mg (n=6)	300 mg (n=6)	400 mg (n=6)	Pooled SEP-631 (n=36)
Any TEAEs, n (%)	5 (41.7)	2 (33.3)	4 (66.7)	0	4 (66.7)	3 (50.0)	1 (16.7)	14 (38.9)
Mild	5 (41.7)	2 (33.3)	3 (50.0)	0	4 (66.7)	2 (33.3)	1 (16.7)	12 (33.3)
Moderate	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (5.6)
Severe	0	0	0	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0	0	0
TEAEs in >1 subject, n (%):								
Headache	1 (8.3)	0	2 (33.3)	0	1 (16.7)	1 (16.7)	0	4 (11.1)
Transaminases increased	1 (8.3)	1 (16.7)	1 (16.7)	0	0	0	0	2 (5.6)
Dysmenorrhoea	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (5.6)

TEAE, treatment-emergent adverse event as number (%)

Safety: Multiple Dose Adverse Event Profile Comparable to Placebo

- **Rate of TEAEs with SEP-631 was comparable with placebo.**
- **No severe or serious events were reported**
- **One mild transaminase elevation (<1.5x ULN) observed with SEP-631 and one observed with placebo**

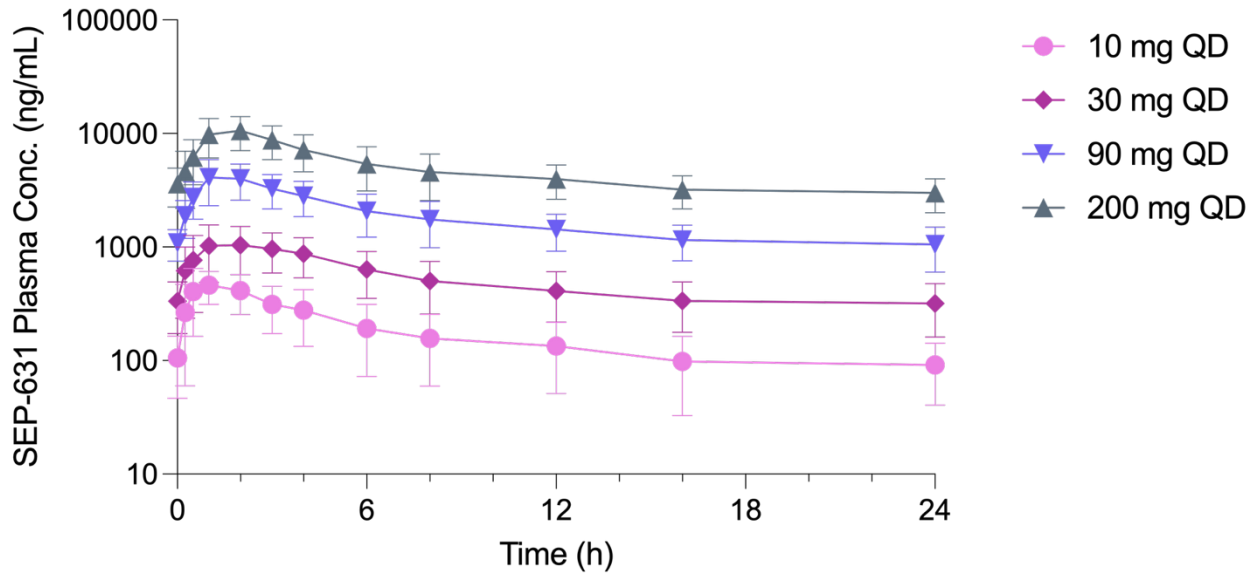
	Pooled placebo (n=15)	SEP-631 Multiple Dose (10 Days)				
		10 mg (n=12)	30 mg (n=12)	90 mg (n=12)	200 mg (n=12)	Pooled SEP-631 (n=48)
Any TEAEs, n (%)	10 (62.5)	3 (25.0)	6 (50.0)	5 (41.7)	4 (33.3)	18 (37.5)
Mild	10 (62.5)	3 (25.0)	6 (50.0)	4 (33.3)	4 (33.3)	17 (35.4)
Moderate	0	0	0	1 (8.3)	0	1 (2.1)
Severe	0	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0
TEAEs in >1 subject, n (%):						
Headache	4 (25.0)	0	2 (16.7)	2 (16.7)	1 (8.3)	5 (10.4)
Dizziness	1 (6.3)	0	0	2 (16.7)	1 (8.3)	3 (6.3)
Abdominal pain	0	2 (16.7)	0	1 (8.3)	0	3 (6.3)
Nausea	1 (6.3)	0	0	1 (8.3)	1 (8.3)	2 (4.2)
Fatigue	1 (6.3)	0	0	1 (8.3)	0	1 (2.1)
Dermatitis contact	1 (6.3)	0	1 (8.3)	0	0	1 (2.1)
ALT or Transaminases increased	1 (6.3)	0	0	0	1 (8.3)	1 (2.1)
Dysmenorrhea	1 (6.3)	0	1 (8.3)	0	0	1 (2.1)

TEAE, treatment-emergent adverse event as number (%)

SEP-631 Pharmacokinetics: Dose-Proportional, Support Once Daily Dosing, and Without Food Effects

- **Approximately dose-proportional exposures were observed across the evaluated dose range**
- **Elimination half-life of SEP-631 is approximately 24 hours, supporting once-daily (QD) dosing**
- **SEP-631 with high-fat, high-calorie meal resulted in similar exposure to fasted conditions (AUC and Cmax)**

Multiple Dose Pharmacokinetics (Day 10)



Pharmacodynamics Assessed Using Icatibant Skin Challenge and AllergyScope™ Detector

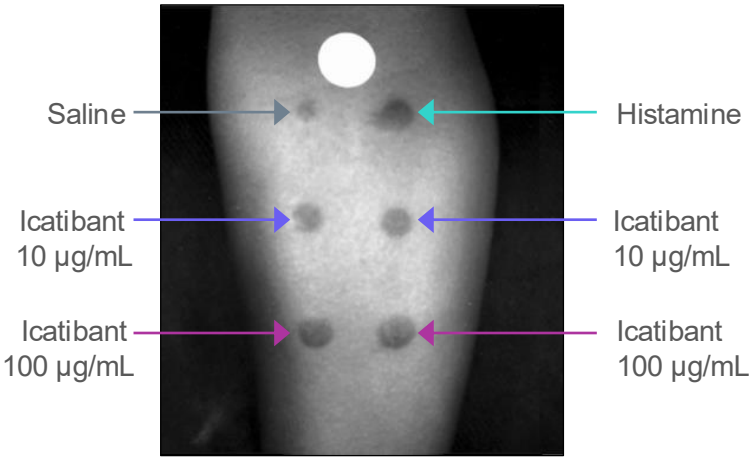
Skin challenge performed at baseline (Day –1) and steady-state (Day 9) following SEP-631 or placebo treatment

- Skin challenge agents: saline (injection control), histamine (wheal positive control), and icatibant at 10 µg/mL and 100 µg/mL (selective MRGPRX2 agonist at low and high concentrations; each performed in duplicate for average measurements)

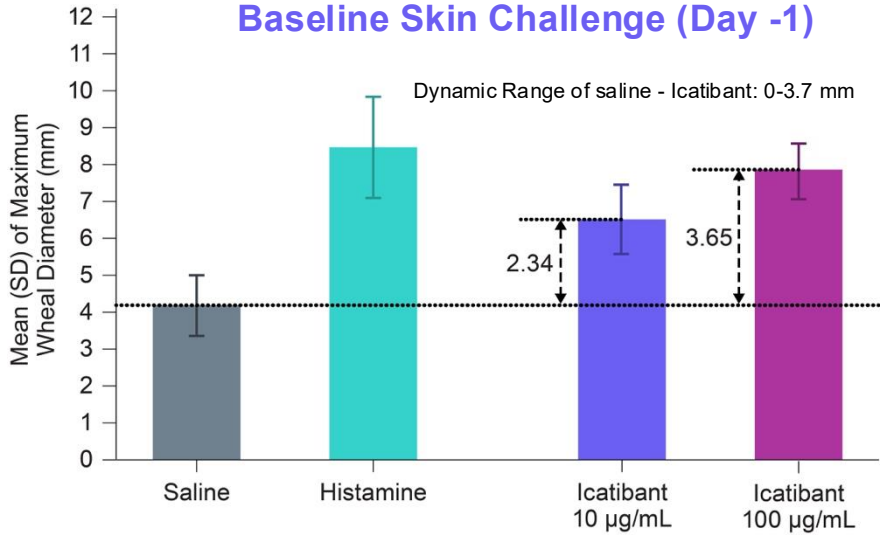
Wheals imaged using AllergyScope™, a precision image-based detector

- Utilizes short-wave infrared (SWIR) spectrum; images transmitted for central lab analysis and adjudication performed by 2 independent and blinded adjudicators at Johns Hopkins University

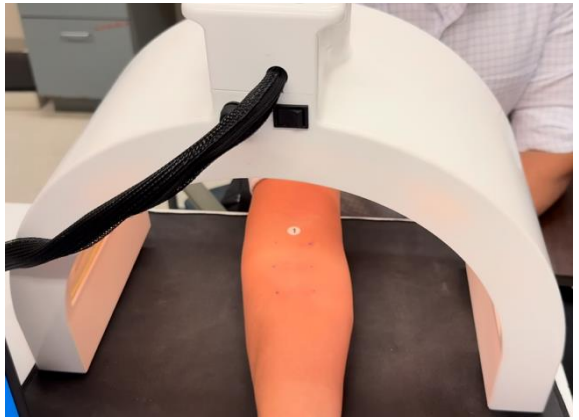
Forearm Intradermal Injection Pattern



Baseline Skin Challenge (Day -1)



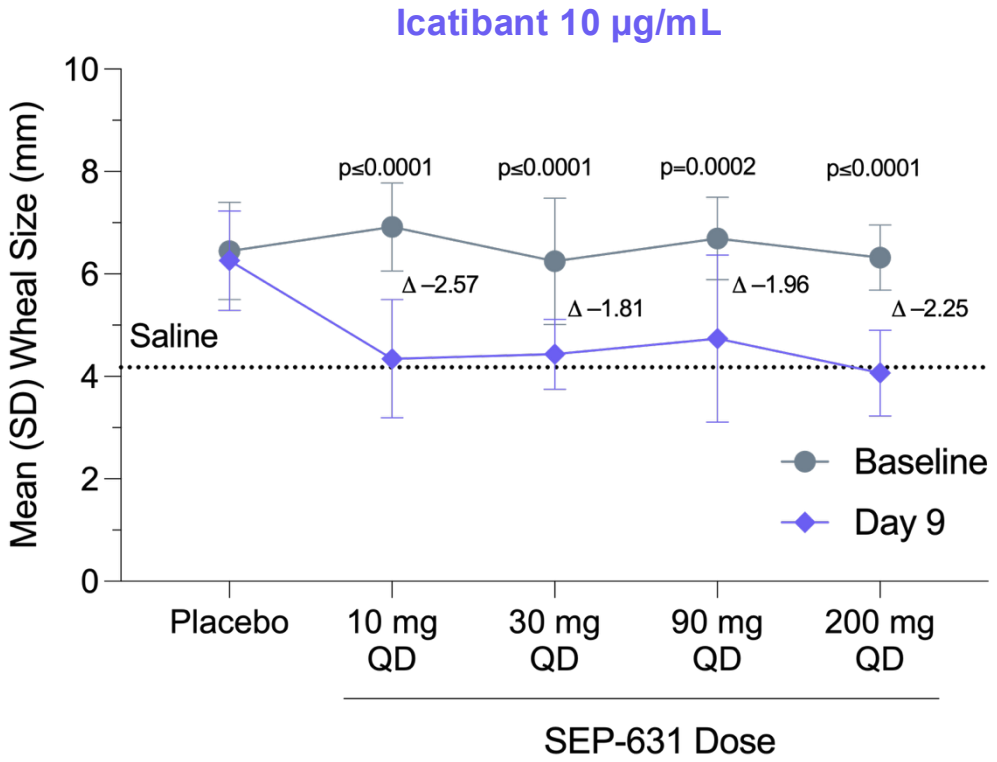
AllergyScope™ Detector

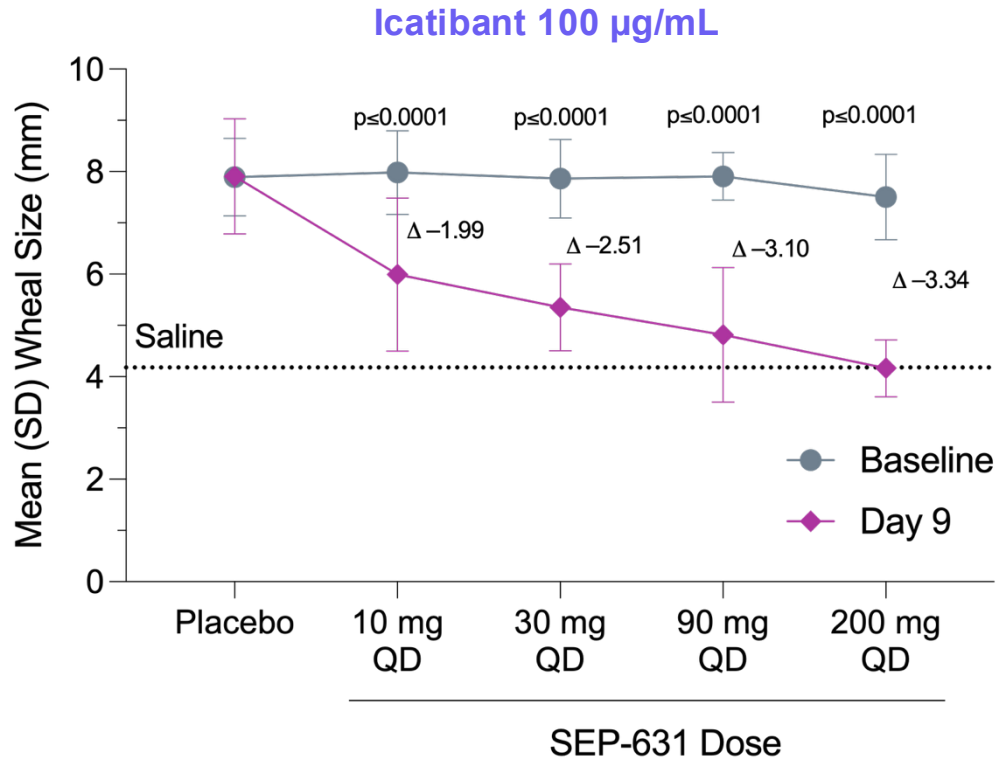


Results depicted as average with error bars represented as standard deviation. Independent wheal measurements yielded between-reader precision of 6% coefficient of variation relative to histamine positive control, indicating a high degree of reproducibility not otherwise possible with traditional manual skin test reading

SEP-631 Inhibits Icatibant Wheal Formation in Dose-Dependent Manner to Complete Inhibition

- **SEP-631 completely inhibited icatibant 10 µg/mL-induced wheals at 10 mg QD, the lowest dose evaluated**
- **SEP-631 inhibited icatibant 100 µg/mL-induced wheals in a dose-dependent manner, with near to complete inhibition at 90 and 200 mg QD**





Nominal p-values comparing each SEP-631 dose level to placebo for change from baseline are based on an ANCOVA model including a fixed effect for treatment group and baseline wheal response as a covariate

Phase 1 Results Support Further Development of SEP-631

SEP-631 was well-tolerated across all studied doses

Pharmacokinetic profile of SEP-631 supports once-daily oral dosing

- Elimination half-life of SEP-631 is approximately 24 hours

SEP-631 treatment resulted in robust inhibition of icatibant-induced skin wheal formation across all studied doses, with complete inhibition observed at doses as low as 10 mg QD (10 µg/mL icatibant challenge)

- Use of the AllergyScope™ detector enabled accurate, precise assessment of skin test wheals
- Inhibition of skin wheals supports SEP-631 engagement with MRGPRX2 in the skin and indicates inhibition downstream signaling and blockade of mast cell degranulation

No clinically meaningful effect of food on SEP-631 exposure, supporting SEP-631 dosing without food restrictions

These Phase 1 results in healthy adult subjects support further clinical evaluation of SEP-631 in patients with mast cell-driven skin diseases, including CSU

SEP-631: Broad Opportunity in Mast Cell-Driven Diseases

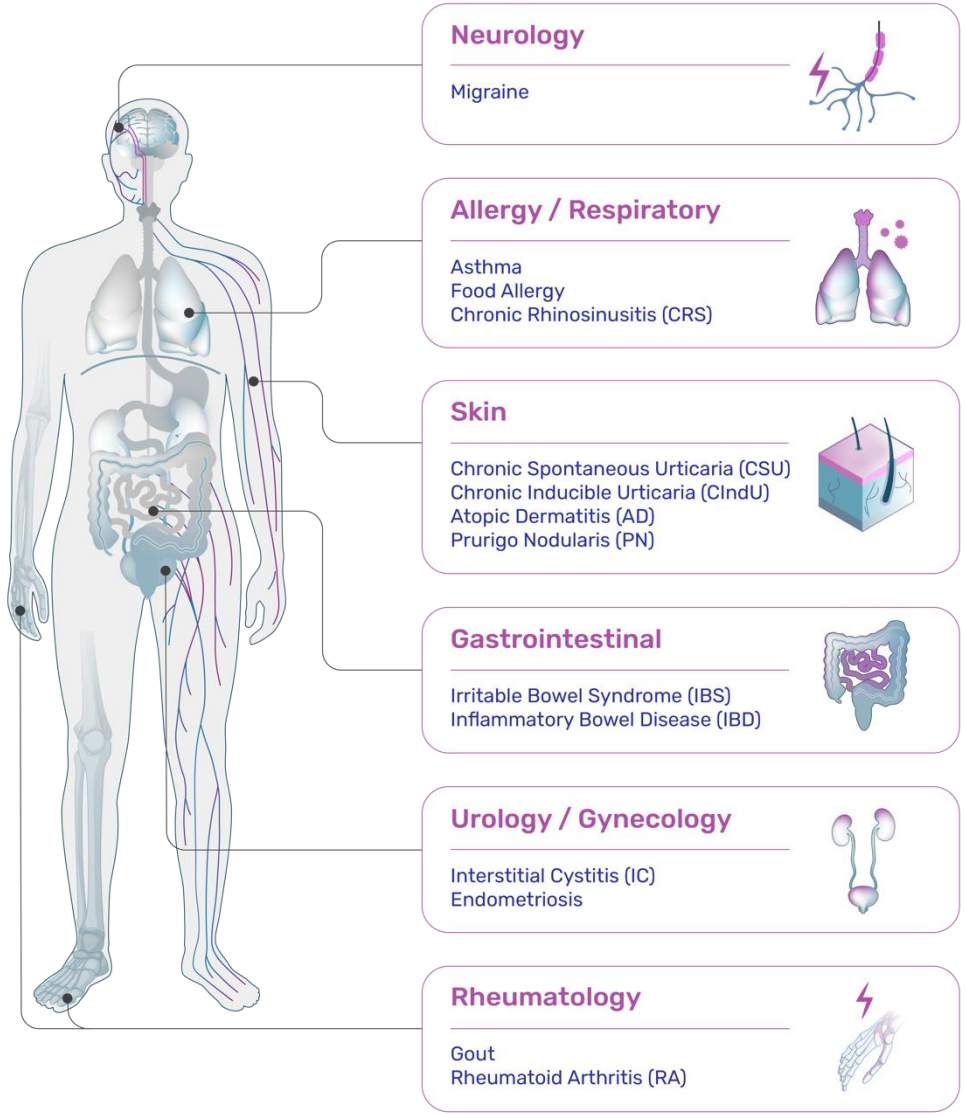
SEP-631 Preclinical Profile Translated Well to Phase 1 Clinical Trial Results

SEP-631 Preclinical Profile	Translation →	Robust SEP-631 Phase 1 Results
• Subnanomolar binding affinity • Slow receptor off-rate kinetics	Target Coverage	• Estimated high receptor occupancy (>99%)
• Excellent oral PK across preclinical species	Pharmacokinetics	• Confirmed QD oral dosing (half-life ~24 hrs) • No food effect, excellent dosing flexibility
• Insurmountable NAM blocks agonist binding pocket for all MRGPRX2 agonists tested	Pharmacodynamics	• Full inhibition of icatibant-induced skin wheal formation at both high and low icatibant doses
• Generally well-tolerated in GLP tox studies • Low DDI risk based on in vitro profiling	Safety	• All AEs considered mild or moderate • No LFT abnormalities or other observations

Potential Best-in-Class Profile of SEP-631:

- Excellent potency with mechanism that provides broad insurmountable inhibition
- Clean clinical safety profile
- Convenient, once daily oral tablet with a flexible dosing schedule

SEP-631: Initial Phase 2 Development Strategy



Since the skin has the highest level of MRGPRX2 expression on mast cells, plan to rapidly advance into Chronic Urticaria studies

- Targeting initiation of a Phase 2b Chronic Spontaneous Urticaria study in 2H 2026
- Pursue open-label Chronic Inducible Urticaria (CIndU) study in symptomatic dermatographism following initiation of the CSU study

Exploring path forward in other high potential indications where tissue mast cells express MRGPRX2 including:

- Atopic Dermatitis
- Interstitial Cystitis / Bladder Pain Syndrome
- Migraine
- Asthma

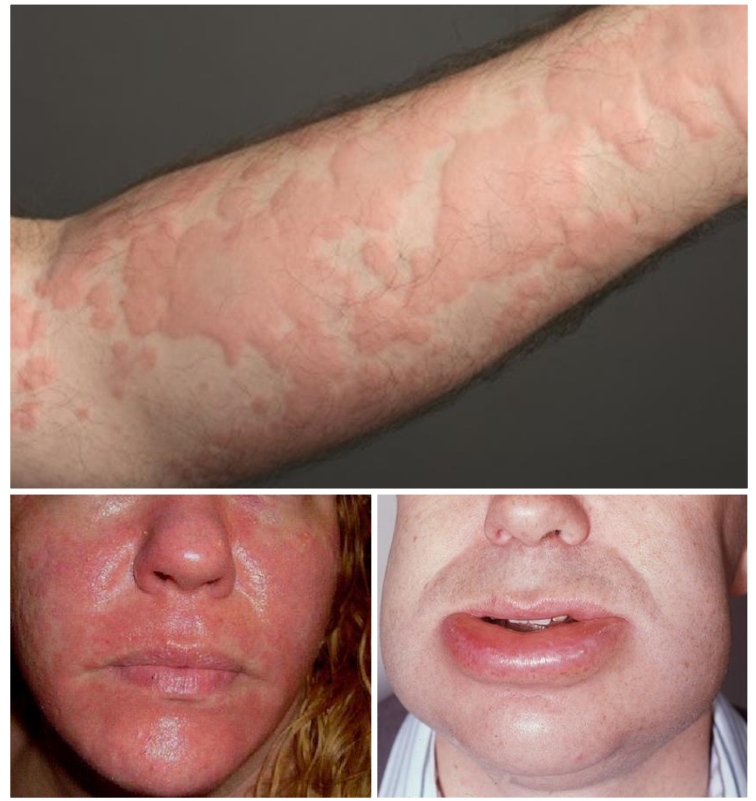
Chronic Spontaneous Urticaria (CSU): High Disease Burden, Large Patient Population

- **CSU is an undertreated dermatology condition characterized by itchy and painful wheals and angioedema**
- **Significant burden of disease; patients experience[1]:**

Disease Burden	% CSU Patients
High to very high impact on their daily life	~40%
Mod-to-severe pain / discomfort	~60%
Mod-to-severe anxiety / depression	~50%
Miss work at least once per week	~20%

- **~40% of patients are refractory to first-line high-dose antihistamines[2-4]**
- **High unmet need for safe second-line oral treatment options**
- **Growing commercial opportunity: ~2-3M CSU patients in the US[5]**

CSU Skin Wheals and Angioedema



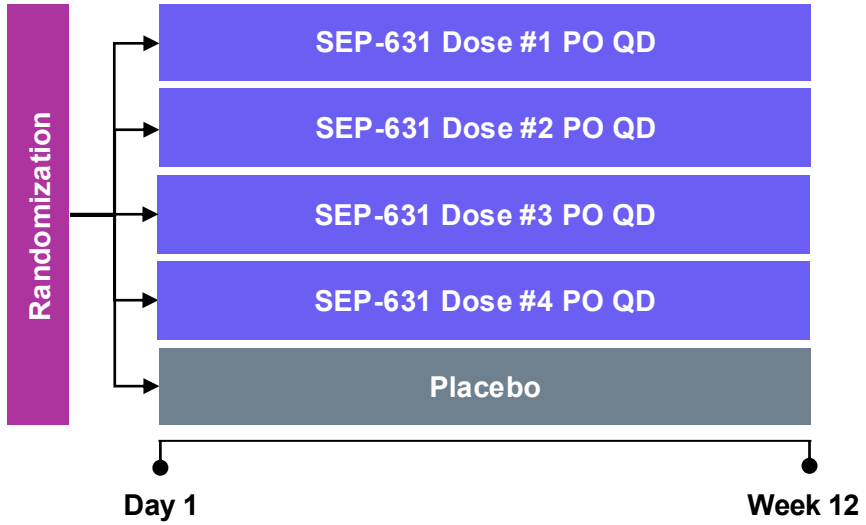
1. ASSURE study, 2. 2022 Kaplan, et al CSU Review article, 3. AWARE study, 4. Guillen et al., 5. GA²LEN task force report

Plan to Initiate Phase 2b Dose-Ranging Chronic Spontaneous Urticaria Study in 2H 2026

- **Long-term GLP toxicology studies in rats and dogs to be completed by mid-year 2026**
- **Planned global, randomized, double-blind, placebo-controlled study to evaluate safety and exploratory efficacy of SEP-631 in CSU**

Patient Population:

- Adults 18 to 65 years
- Moderate to Severe CSU
- Remain symptomatic on second-generation H1 antihistamine



Primary Endpoint:

- Change from baseline in UAS7 at Week 12

Key Secondary Endpoints:

- Safety / Tolerability
- UAS7≤6 and UAS7=0
- Change in ISS7
- Change in HSS7

- **Following initiation of the CSU study, we plan to pursue an open-label Chronic Inducible Urticaria (CIndU) study**

UAS7: Urticaria Activity Score over 7 days; ISS7: Itch Severity Score over 7 days; HSS7: Hives Severity Score over 7 days

Exploring Opportunities for SEP-631 in Additional Indications with High Unmet Need

- **Indications characterized by mast cells playing a central role in disease pathology and evidence of MRGPRX2 expression on tissue-resident mast cells**
- **Indications cover breadth of target organs and have different pathologies and unmet needs**
- **Developing cost-efficient and right-sized clinical strategies to demonstrate SEP-631 benefit**

Atopic Dermatitis

- >10M moderate to severe AD patients[1,2]
- MRGPRX2 could play a central role in itch resolution
- Safe, oral treatment would grow market

Interstitial Cystitis

- ~1-4M interstitial cystitis patients[3]
- No compelling treatment options
- Bladder has second highest level of MRGPRX2 expression after skin

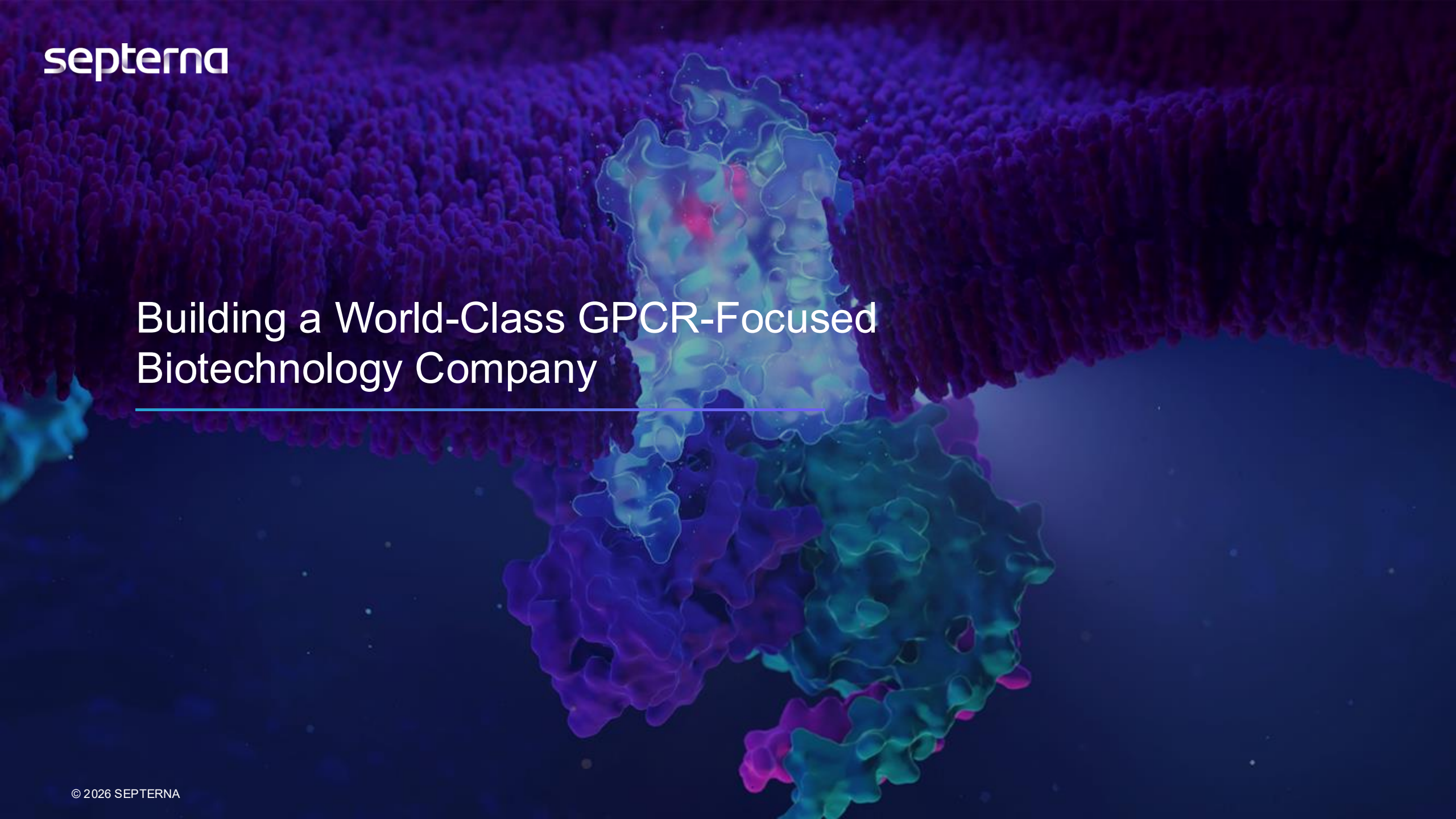
Migraine

- ~15-25M moderate-to-severe migraine patients[4]; ~40% would benefit from preventative treatment[5]
- Current therapies provide only modest efficacy and drug cycling is common

Asthma

- ~1-3M severe asthma patients[6,7]
- High unmet need for safe, oral treatment

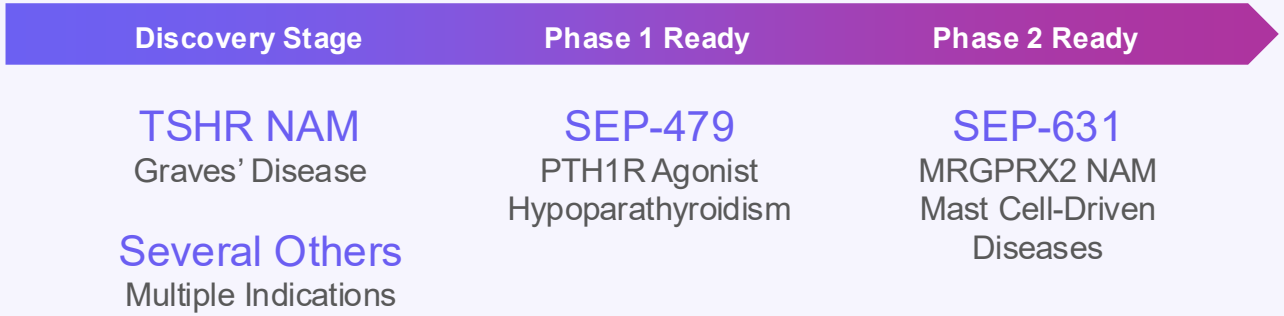
Estimates are US addressable patients. 1. National Eczema Association, 2. 2019 Fuxench, et al, 3. 2022 Anger, et al, 4. 2024 Cohen, et al, 5. 2021 American Headache Society Consensus Statement, 6. ACAAI, 7. 2020 Wang, et al



Building a World-Class GPCR-Focused Biotechnology Company

Septerna: Building a World-Class GPCR-Focused Biotechnology Company

- **SEP-631 Phase 1 results provides clear validation of Septerna's Native Complex Platform®**
  - Identification of novel binding pockets to mechanistically modulate GPCRs in therapeutically meaningful ways including unlocking new modes of action such as insurmountable NAMs to generate drug candidates with best-in-class profiles
  - Ability to use structure-based drug design to optimize clinical candidates with targeted pharmaceutical properties
- **Septerna is building a robust pipeline of GPCR-targeted medicines**
  - Multi-product wholly-owned pipeline, each with a multi-billion $ market opportunity
  - Leveraging Native Complex Platform® to fuel additional programs through partnerships (Novo collaboration)
  - Well-capitalized with cash runway expected to support operating plans at least into 2029



Pioneering a New Era of GPCR Drug Discovery