

Pioneering a New Era of GPCR Drug Discovery

Corporate Presentation

August 2026

Nasdaq: SEPN

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Forward-Looking Statements

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

Native Complex Platform® designed to unlock the full potential of GPCR therapies

- Iterative structure-based drug design to rapidly optimize and validate programs in animal models

Portfolio strategy to drive value creation

- Validated targets + early clinical readouts + multi-billion $ market opportunities

Well-capitalized

- Cash runway expected to support operating plans at least into 2029

Lead Programs

SEP-479 PTH1R Agonist: Potential first-in-class oral small molecule for hypoparathyroidism; Phase 1 in healthy volunteers initiated with SAD/MAD data anticipated in Q1 2027

SEP-631 MRGPRX2 NAM: Pipeline-in-a-product opportunity for mast cell-driven diseases; Phase 1 demonstrated robust PD with QD dosing; evaluating multi-indication clinical signal-finding strategy

Discovery Stage

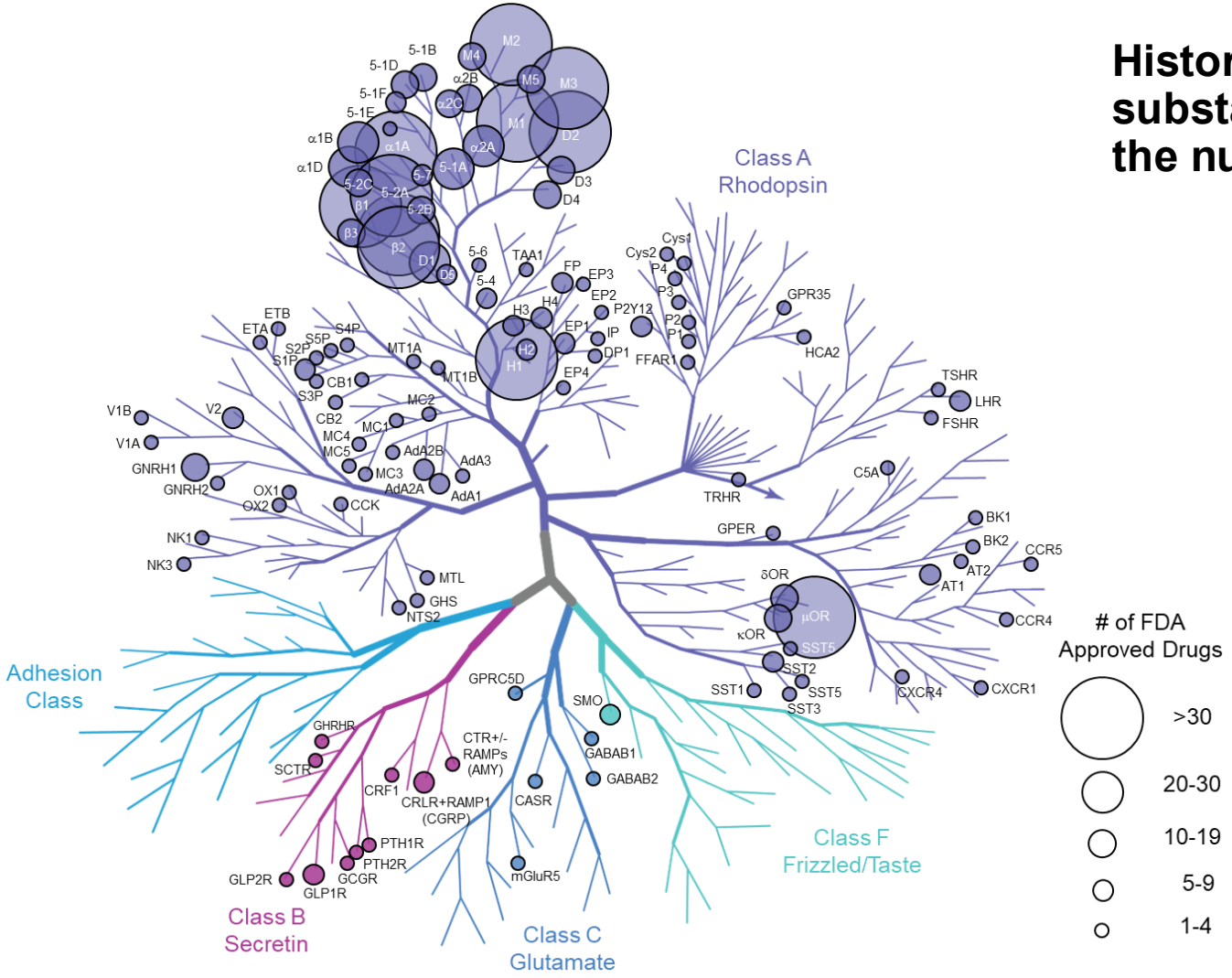
TSHR NAM: Potential disease-modifying treatment for Graves' disease and TED; progressing multiple lead compounds toward development candidate selection

Incretin Receptor Agonists: Potential multi-billion $ collaboration with Novo Nordisk for oral small molecules for metabolic diseases

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GPCR: G protein-coupled receptor; NAM: negative allosteric modulator; TED: thyroid eye disease

GPCR Drug Discovery Success Has Been Highly Concentrated to a Small Fraction of GPCRs



Historically productive target class, yet substantial untapped opportunity to expand the number of druggable GPCRs

~1/3 of all FDA-approved drugs (~500 approved products) target GPCRs

>70% of GPCR drugs target 6 small subfamilies of GPCRs

~75% of potential GPCR targets remain undrugged

Our focus: Unlocking difficult-to-drug GPCRs with our Native Complex Platform®

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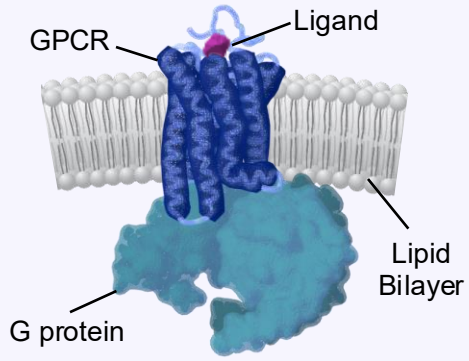
Proprietary Native Complex Platform®

Today's GPCR Drug Discovery Challenge

- Several new small molecule drug discovery technologies have largely been inaccessible to GPCRs
- Inability to isolate fully functional GPCR proteins significantly limits use of modern discovery tools

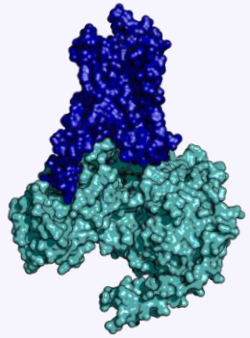
Native Complex Platform® : Industrialized Workflows to Unlock Difficult-to-Drug GPCRs

Native Complexes



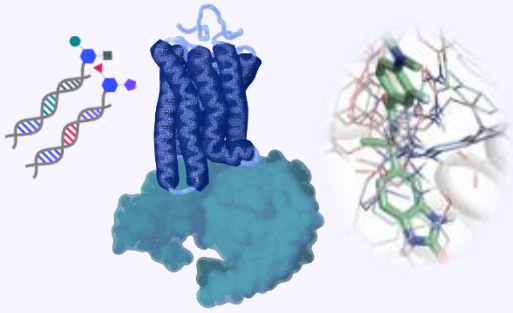
Retain GPCR natural structure, function, and dynamics

High-Resolution GPCR Structures



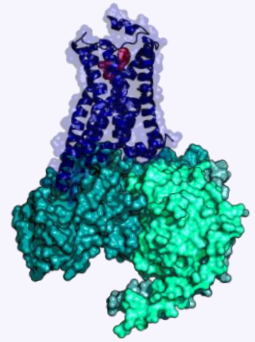
Novel binding pockets and new insights into GPCR modulation

Technologies to Screen Billions of Compounds



Discovery of new leads with relevant modes of action

Structure-Based Drug Design & Optimization

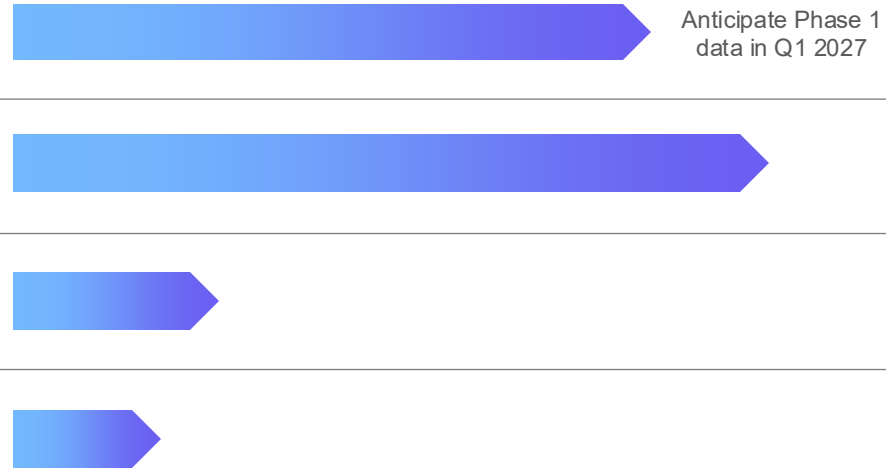


<1 year from initiation of med chem to activity in animal models for each program to date

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

Wholly-Owned Programs		Development Status			
Program / Target Mode of Action	Therapeutic Area Indications	Discovery	IND-enabling	Phase 1	Phase 2
SEP-479 (PTH1R) Agonist	Endocrinology Hypoparathyroidism				
SEP-631 (MRGPRX2) Negative Allosteric Modulator	Immunology and Inflammation Mast cell-driven diseases				
TSHR Program Negative Allosteric Modulator	Endocrinology Graves' disease & Thyroid eye disease				
PTH1R Program Agonist	Endocrinology Osteoporosis				



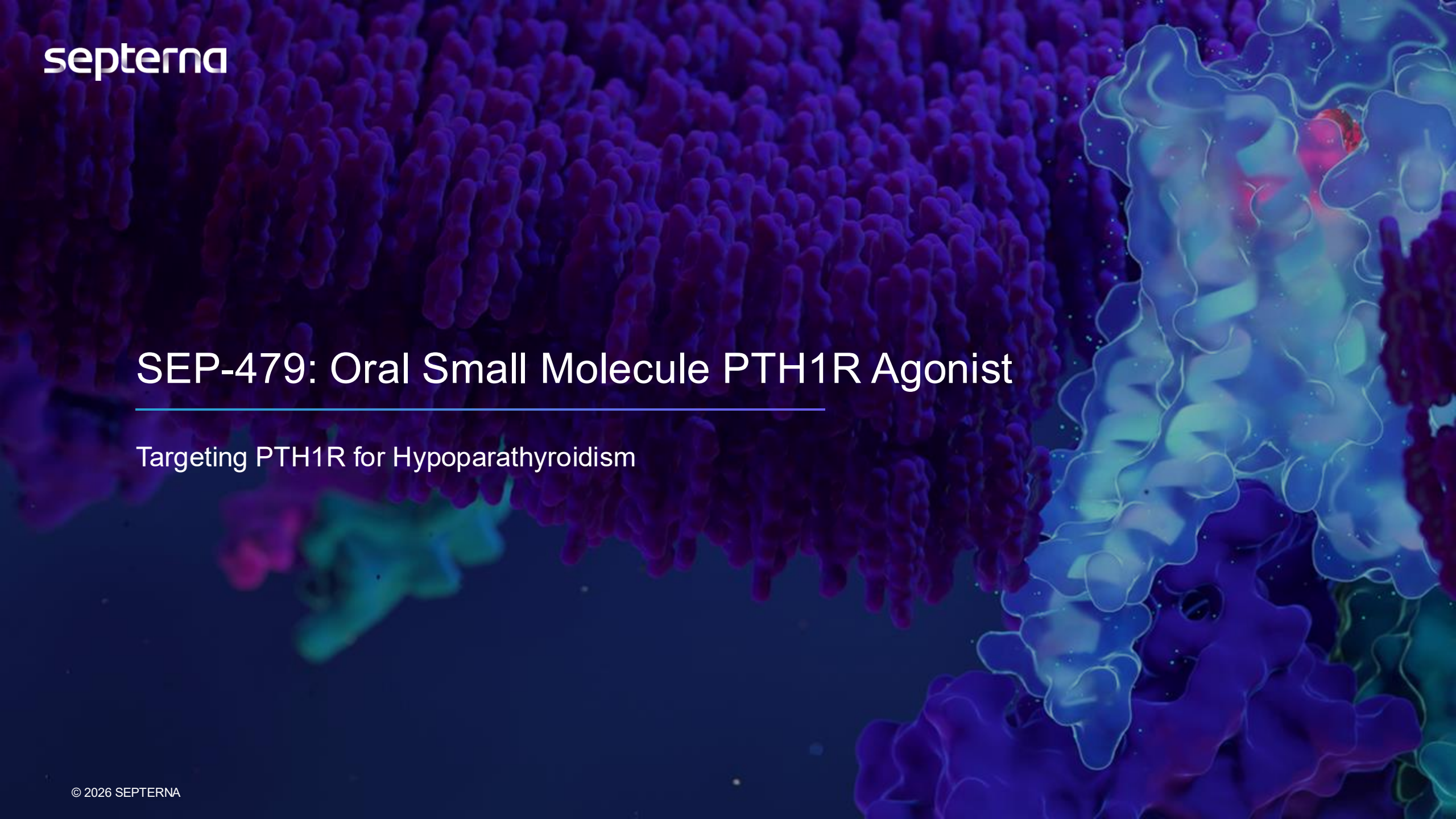
Research Areas:

Neurology, Women's Health, Cardiovascular Disease and Respiratory Disease

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

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* Partnership also includes two undisclosed targets



SEP-479: Oral Small Molecule PTH1R Agonist

Targeting PTH1R for Hypoparathyroidism

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Hypoparathyroidism: Significant Unmet Need for an Oral PTH Replacement

Hypoparathyroidism: Low PTH leads to low blood calcium

- ~70K patients in US; ~140K patients in EU

Challenging patient symptoms

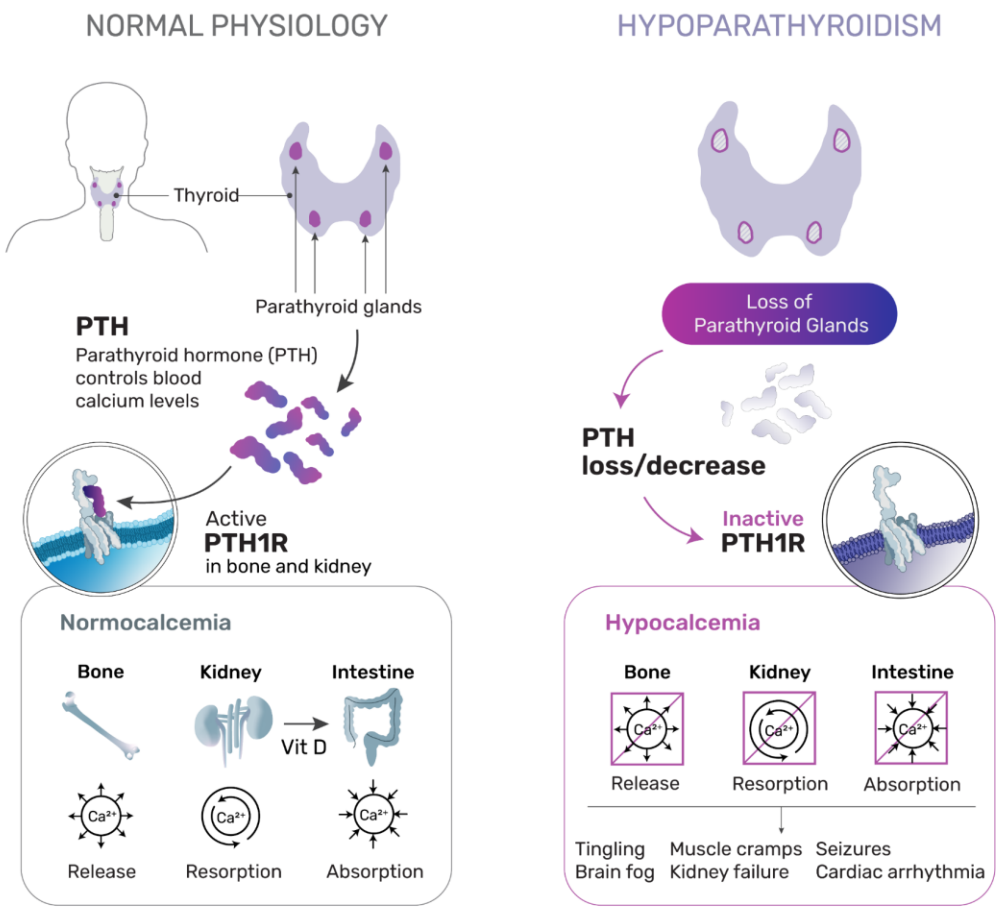
- Muscle cramps, tingling, brain fog
- Life-threatening complications: cardiac arrhythmias, seizures

Standard-of-care limitations

- Calcium supplements (high doses several times per day) and Vitamin D do not fully resolve symptoms and lead to complications including calcifications and renal impairment
- Approved injectable PTH therapy will require life-long daily injections

Our Strategy: Functionally replace PTH with oral small molecule PTH1R agonist to normalize serum calcium

PTH: Master Regulator of Blood Calcium



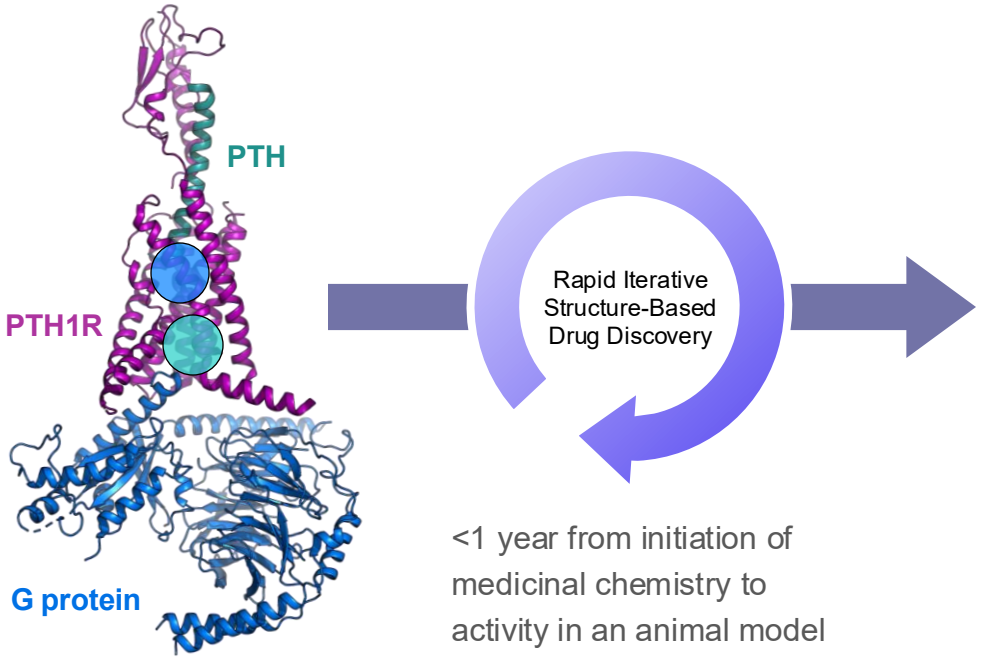
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PTH: Parathyroid Hormone

SEP-479: Discovered with Native Complex Platform® as Potent Oral PTH1R Agonist for Hypoparathyroidism

Native Complex Hit Identification and Structure-Based Optimization

Multiple PTH1R agonists with distinct binding sites identified and optimized in parallel to candidate quality molecules



<1 year from initiation of medicinal chemistry to activity in an animal model

SEP-479: Clinical Candidate

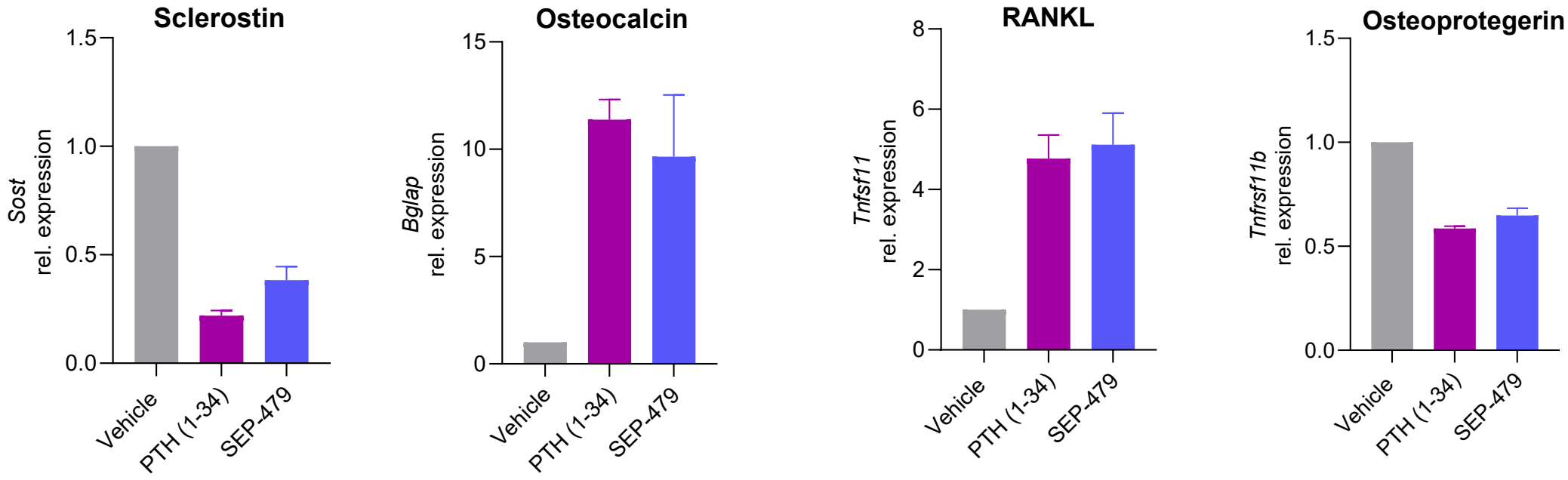
- Potent oral small molecule PTH1R agonist
- Demonstrated comparable effects to PTH peptides in cell-based assays and in vivo models
- Normalized serum calcium in preclinical rat surgical model of hypoparathyroidism
- Monkey PK/PD study demonstrated robust decreases in endogenous PTH and increases in serum calcium
- Excellent pharmaceutical properties; projected to achieve full-day HypoPT control with QD dosing
- Generally well tolerated in GLP toxicology studies

Phase 1 in healthy volunteers is in progress

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SEP-479: A Potent PTH1R Agonist Demonstrated Pharmacologic Responses Similar to PTH peptide in Cell-Based Assays

Gene expression analysis comparing SEP-479 to PTH (1-34) in bone cell line demonstrated similar PTH1R-mediated pharmacologic responses



- Suppressed sclerostin and upregulated osteocalcin expression, suggesting promotion of osteoprogenitor differentiation and enhancement of bone formation
- Increased RANKL and decreased osteoprotegerin transcription, suggesting promotion of osteoclast differentiation and acceleration of bone resorption

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Methods: UMR-106 cells were treated with PTH (1-34) or SEP-479 for 5 hours; gene expression analyzed by quantitative RT-PCR; SEP-479: 10 nM; PTH (1-34): 0.1 nM

SEP-479 Normalized Serum Calcium and Phosphate in Rat Hypoparathyroidism Model

Rat surgical model of hypoparathyroidism



Rat

↓ Surgery to remove parathyroid glands

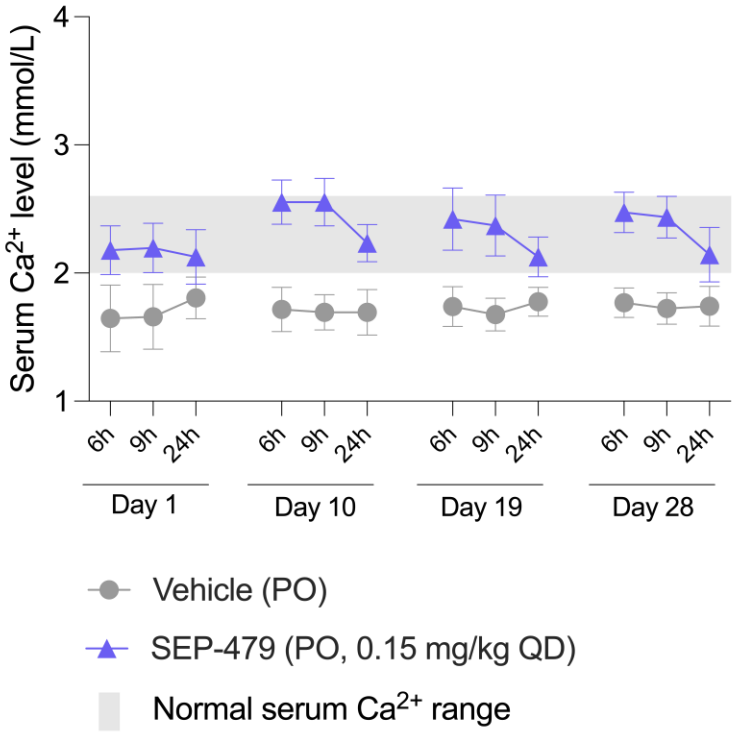
Decreased serum calcium (hypocalcemia)

↓ Oral small molecule PTH1R agonist

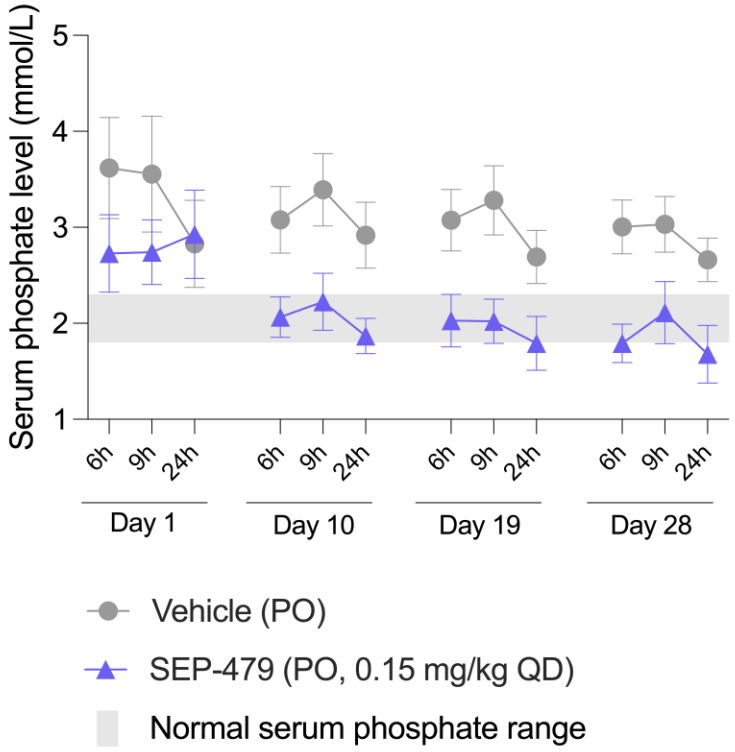
Normalize serum calcium

SEP-479: 28-day Oral QD Dosing

Sustained Normalization of Serum Ca^{2+} Levels



Sustained Normalization of Serum Phosphate Levels



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PO: oral dosing QD: once daily dosing

SEP-479 Improved Renal Mineral Homeostasis and Engaged Bone Remodeling in Rat Hypoparathyroidism Model

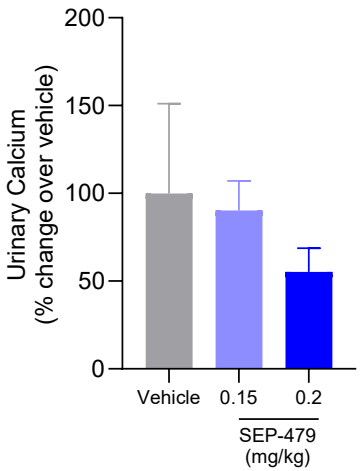
SEP-479 demonstrated PTH-like renal pharmacology profile:

- Decreased urinary calcium concentration and increased active Vitamin D production

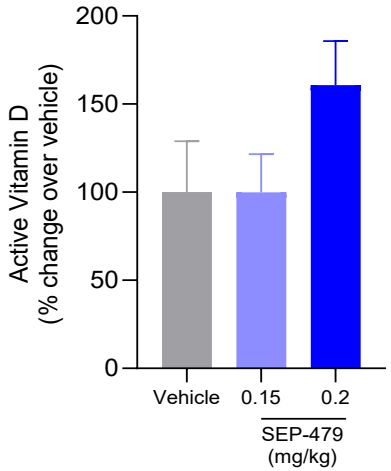
SEP-479 demonstrated PTH-like bone remodeling effects:

- Decreased bone mineral density, increased CTX (serum bone catabolic marker) and modestly changed P1NP (serum bone anabolic marker)

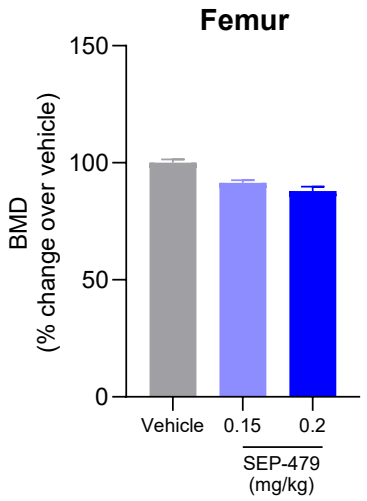
Urinary Calcium

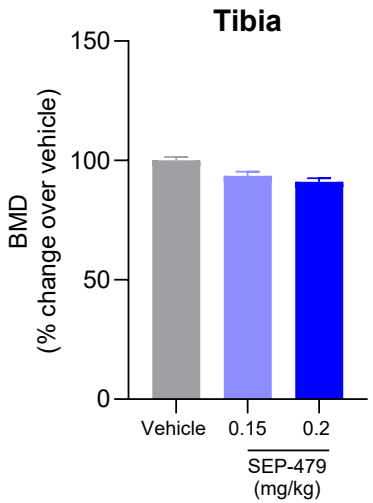


Active Vitamin D

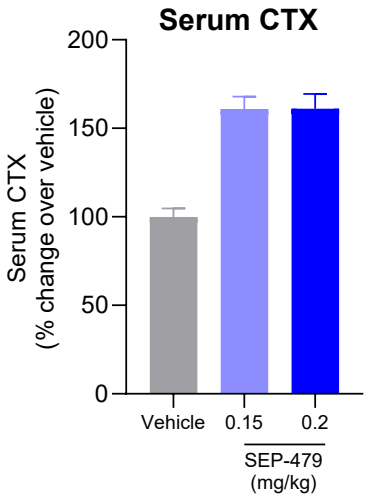


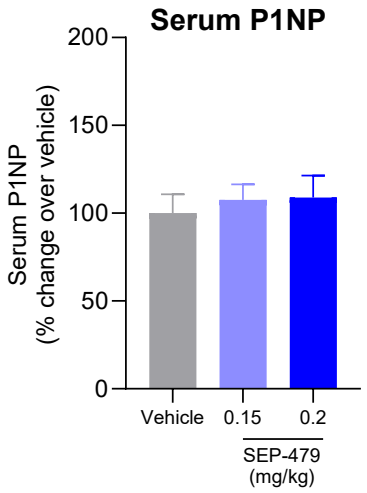
Bone Mineral Density





Serum Bone Biomarkers





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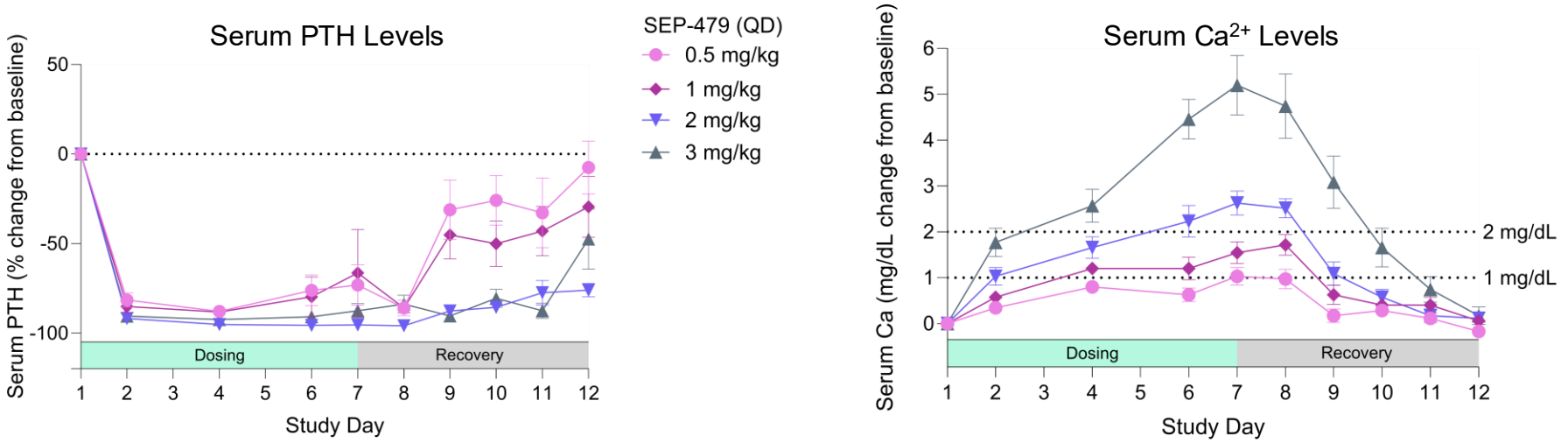
CTX: C-terminal telopeptides of type 1 collagen; P1NP: Procollagen type 1 N-terminal propeptide

SEP-479 Lowered Endogenous PTH and Increased Serum Calcium In Healthy Cynomolgus Monkey Pharmacodynamic Study

In healthy animals (and humans) with normal parathyroid gland function:

- Treatment with PTH agonists leads to rapid suppression of endogenous PTH secretion to maintain normal calcium levels
- When feedback suppression of endogenous PTH reaches its limits, PTH agonist therapy at higher doses leads to calcium increases

SEP-479: 7-day Healthy Cynomolgus Monkey Pharmacodynamic Study



Lessons from PTH peptide clinical trials:

- Doses in healthy subjects that increase calcium ~0.5-1 mg/dL translated to relevant therapeutic pharmacology in hypoparathyroidism patients

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SEP-479 Preclinical Profile Supported Advancement into Phase 1

Potent oral small molecule PTH1R agonist

- Demonstrated effects comparable to PTH peptides in cell-based assays and in vivo models

Pharmacokinetic studies

- Demonstrated high oral bioavailability and long half-life following oral dosing across preclinical species (mouse, rat, dog, cyno)
- Projected human half-life was approximately 40-80 hours with potential to support QD human dosing

Non-clinical safety studies

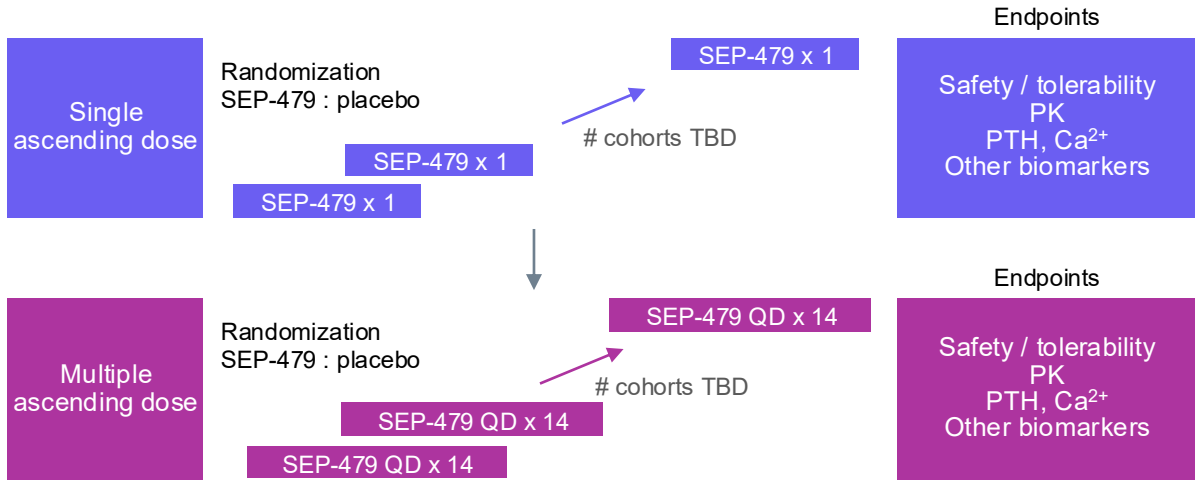
- Generally well tolerated in three non-clinical safety studies (28-day GLP toxicology in rats, dogs, cyno)
- Dose-limiting effect in each species was on-target hypercalcemia, as expected for a PTH1R agonist

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SEP-479 Phase 1 Study in Healthy Volunteers is in Progress

Study design:

- Randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy adult volunteers
- Will also include a cross-over food effect study
- Estimated enrollment: up to ~150 subjects (in Australia)



SEP-479 dose escalation in healthy volunteers is ongoing:

- Observed elimination half-life is ~3-4 days which we believe should support once-daily dosing
- MAD cohort dosing duration of 14 days planned to adequately assess steady-state PK

Translation of healthy volunteer studies to hypoparathyroidism patients:

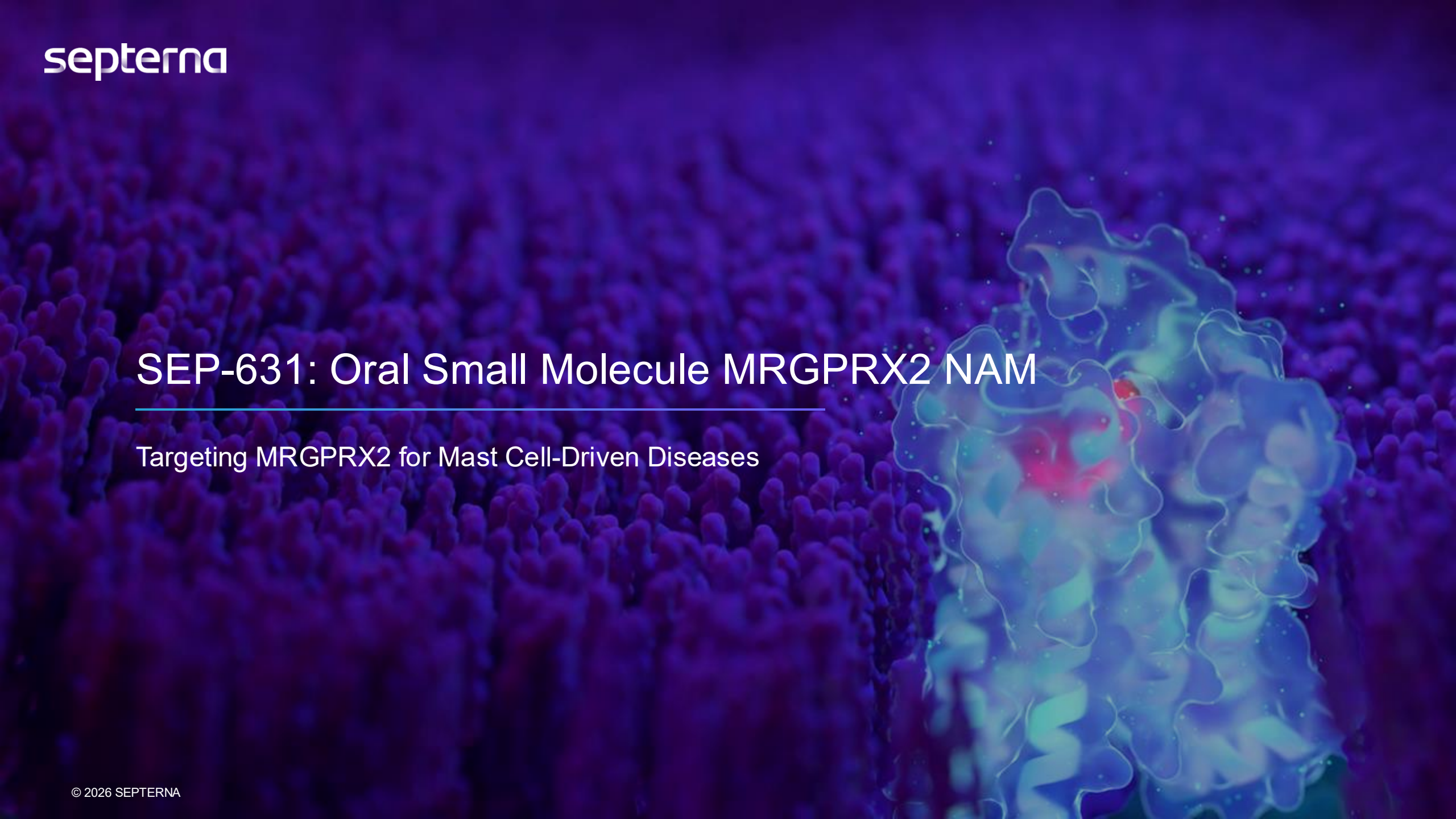
- Healthy subjects and hypoparathyroidism patients both have intact PTH1R in the bone and kidneys to control serum calcium
- Injectable PTH peptide trials: changes in serum calcium translated well from healthy volunteers to hypoparathyroidism patients
- On-target pharmacology in Phase 1 to be confirmed initially with decreases in endogenous PTH, and at higher doses, with increases in serum calcium

Anticipate SEP-479 SAD / MAD results in Q1 2027

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SEP-631: Oral Small Molecule MRGPRX2 NAM

Targeting MRGPRX2 for Mast Cell-Driven Diseases



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

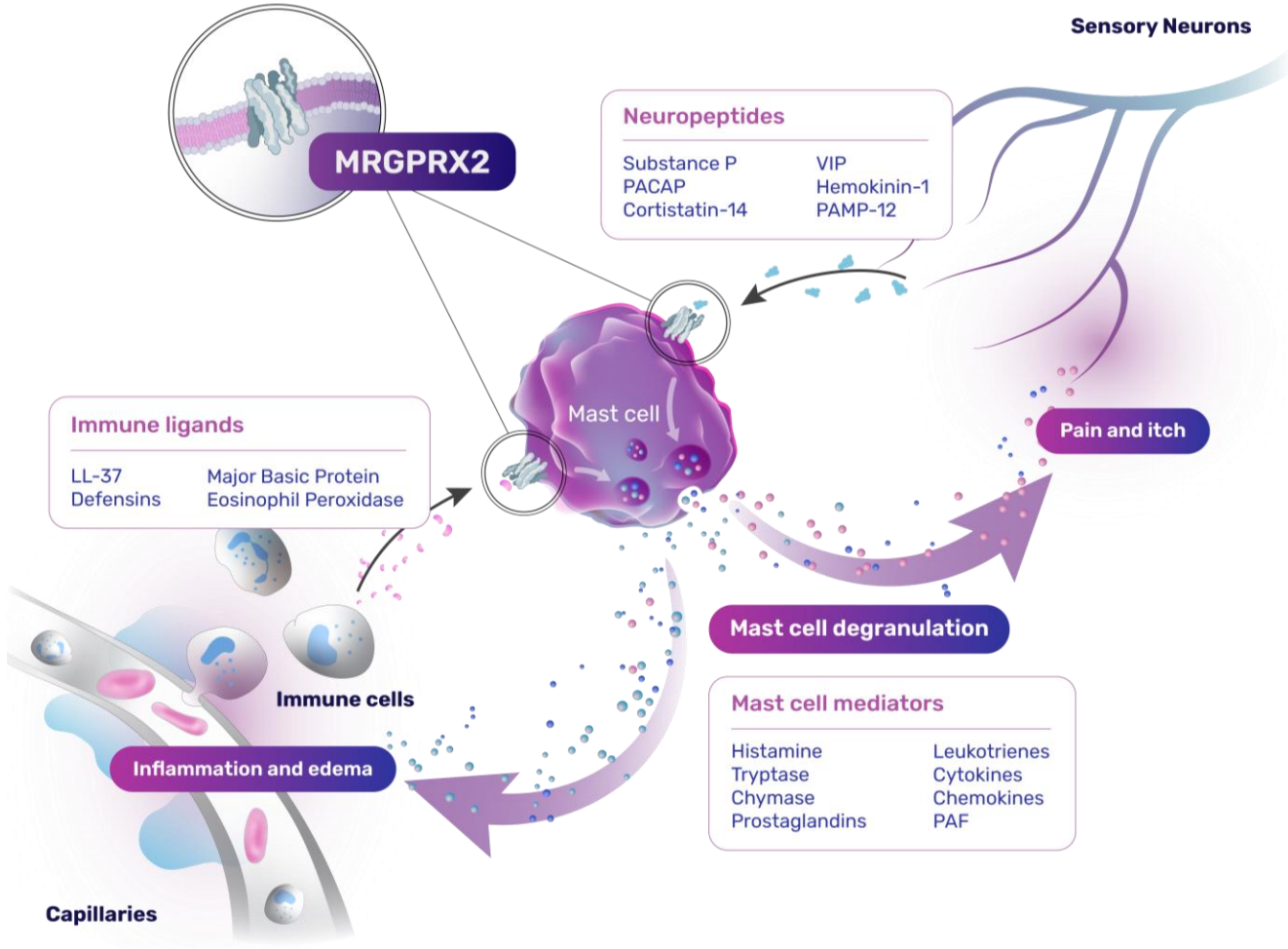
MRGPRX2 is activated by a host of endogenous agonists leading to IgE-independent mast cell degranulation

- 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



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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

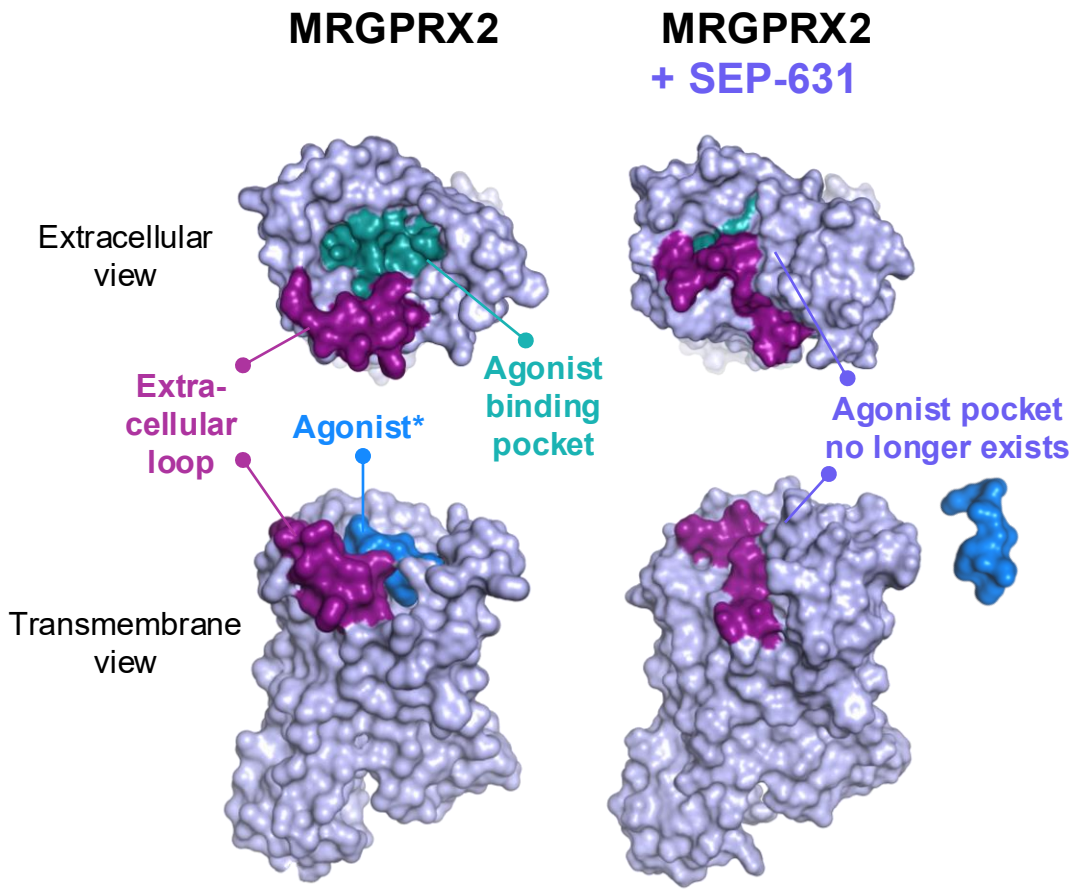
- Very high binding affinity (Ki ~0.5 nM)
- Slow dissociation rate ($t_{1/2}$ > 2 hours)

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

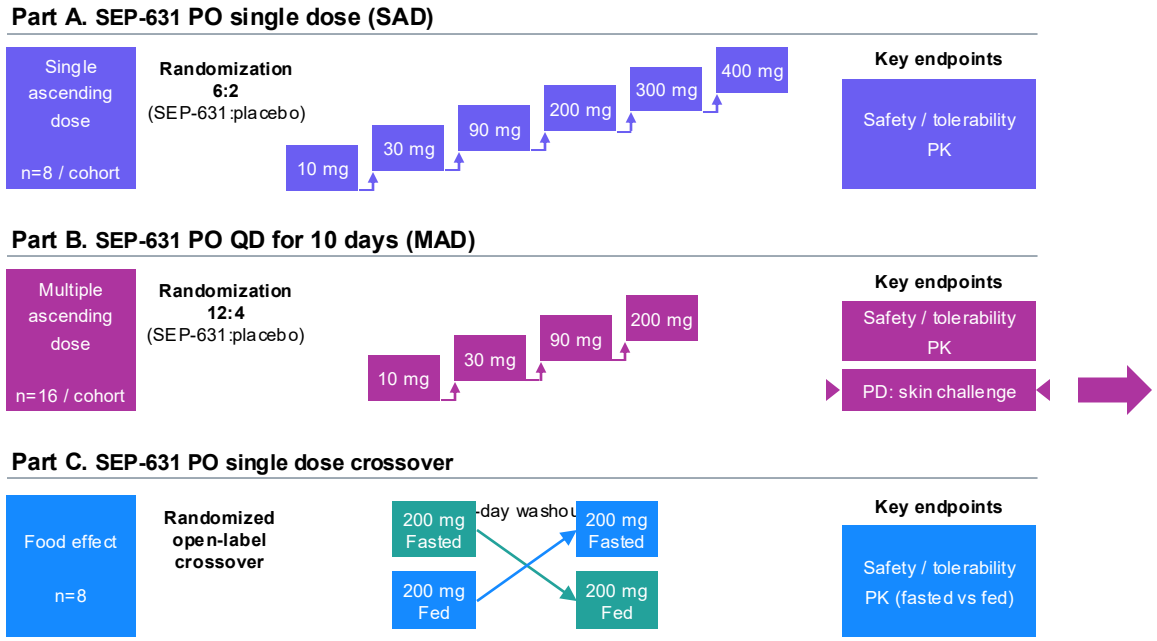
SEP-631 Induces a Structural Change in MRGPRX2 That Completely Closes the Agonist Binding Pocket

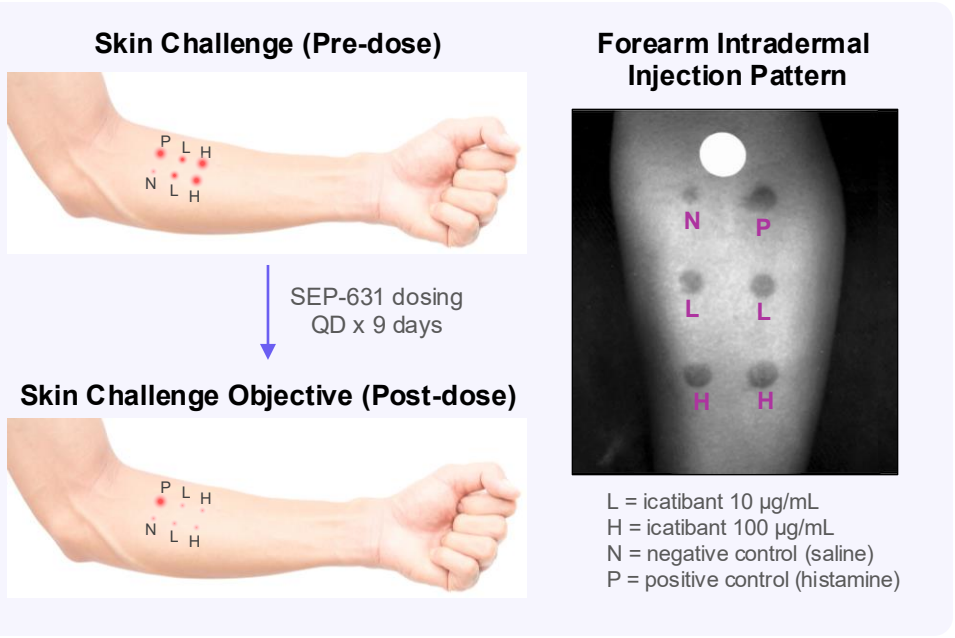


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*Cortistatin-14

SEP-631 Phase 1 SAD / MAD Demonstrated Safety, Robust Pharmacodynamics, and PK to Support Once-Daily Oral Dosing





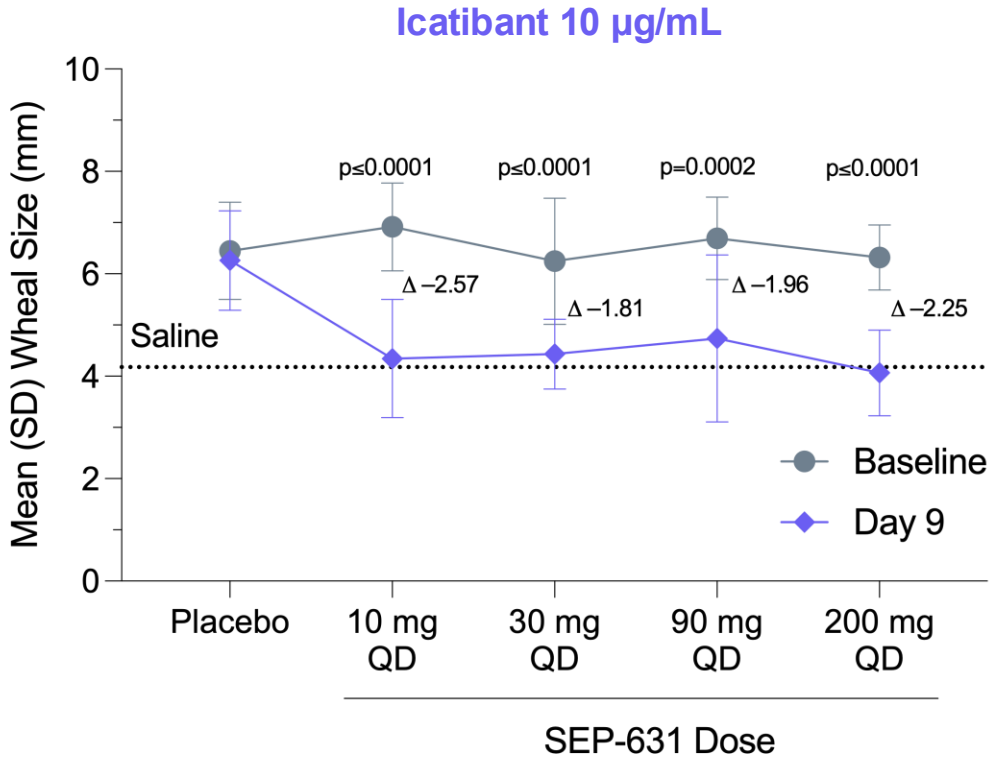
Phase 1 Results

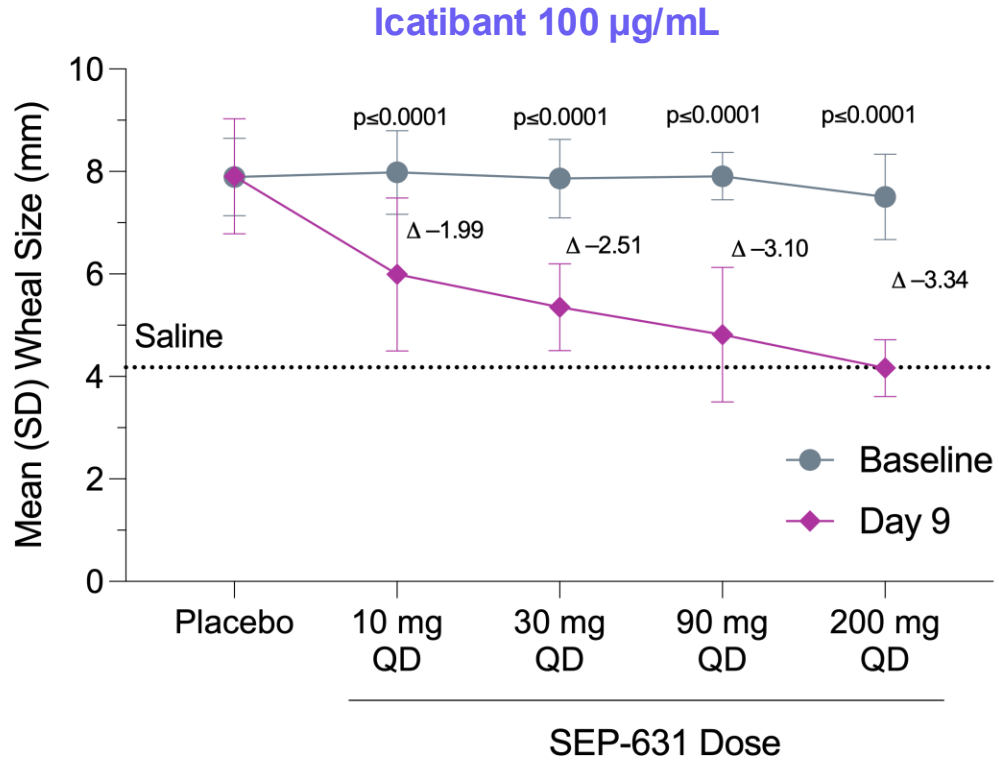
- **Safety:** No severe or serious events; rate of adverse events with SEP-631 was comparable with placebo
- **Pharmacokinetics:** Elimination half-life is approximately 24 hours, supporting once-daily (QD) dosing
- **Food effect study:** Similar exposure in fed and fasted conditions supports QD dosing without food restrictions
- **Pharmcodynamics:** Robust inhibition of icatibant-induced skin wheal formation

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SEP-631 Inhibited 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**





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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

SEP-631 Preclinical and Phase 1 Data Supports Potential Best-in-Class Profile

Full inhibition of MRGPRX2 activation + Oral once-daily tablet and clean safety profile → Potential to translate into best-in-class efficacy for multiple disease indications

NAM mechanism provides broad insurmountable MRGPRX2 inhibition

- Subnanomolar binding affinity (Ki ~0.5 nM) with slow receptor off-rate kinetics ($t_{1/2}$ > 2 hours)
- Completely closes MRGPRX2 agonist binding pocket, preventing agonist binding

Robust clinical pharmacodynamic effects

- High receptor occupancy (>99%) translated into full inhibition of icatibant-induced skin wheal formation in Phase 1, and similarly high levels of MRGPRX2 inhibition in target tissues throughout the body may be needed for optimal efficacy for mast cell-driven diseases

Clean clinical safety profile

- No severe or serious events observed; rate of adverse events with SEP-631 was comparable with placebo

Convenient, once-daily oral tablet with a flexible dosing schedule

- Elimination half-life ~24 hours; no food effect

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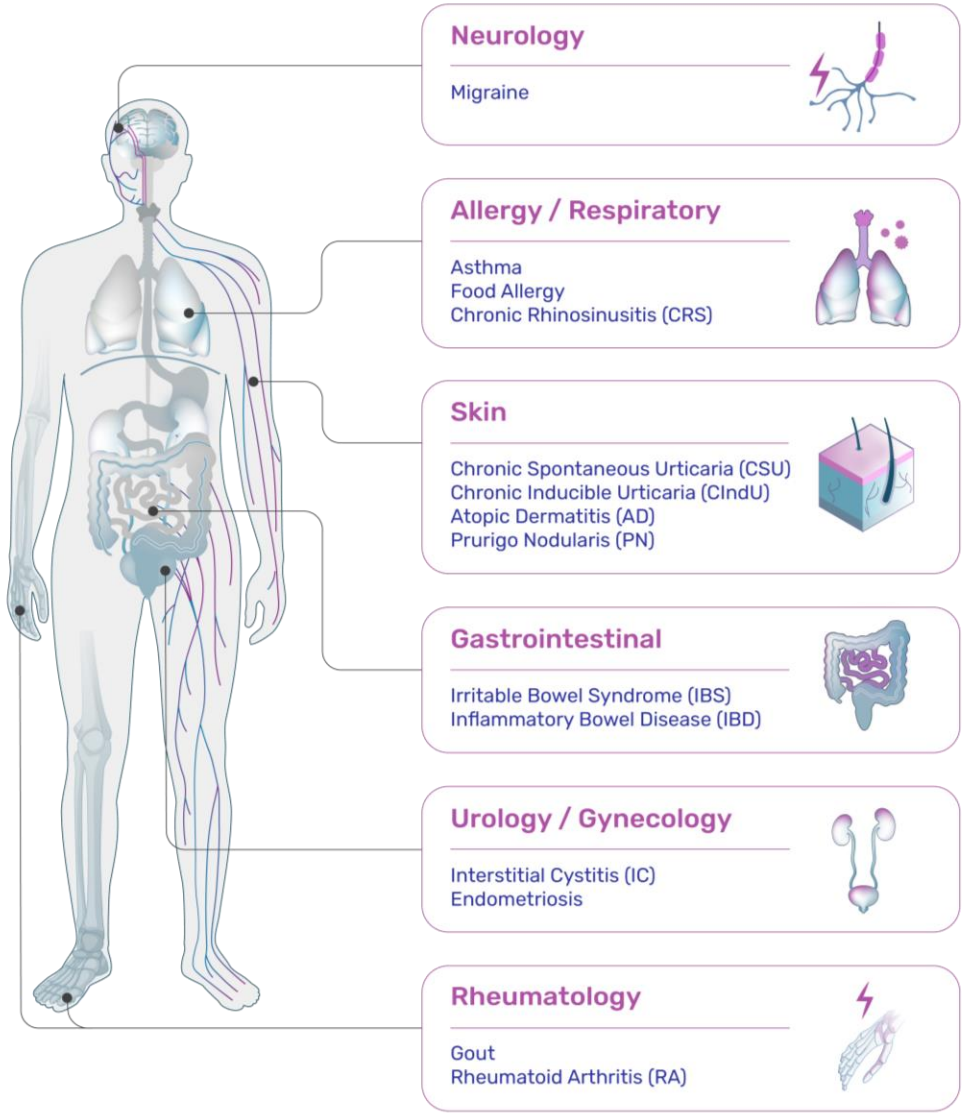
SEP-631: Clinical Development Strategy

Broad opportunity across a range of allergic and inflammatory diseases where mast cells are implicated in disease pathophysiology

Near-Term Strategy: Explore opportunities for SEP-631 in multiple indications with capital-efficient and right-sized signal-finding clinical studies

Focus on indications characterized by:

- Diseases where mast cells are believed to play a central role
- Diverse pathologies to test various therapeutic hypotheses
- Significant unmet need



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TSHR NAM Program

Oral Small Molecule Targeting TSHR for Graves’ Disease and TED

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No Disease-Modifying Therapies for Graves' Disease and Thyroid Eye Disease (TED)

Graves' Disease & TED Pathophysiology:

- Autoantibodies activate TSHR in thyroid gland and in orbital fibroblasts behind the eyes

Graves' Disease

- >2M patients in US
- Standard-of-care: antithyroid drugs, radioactive iodine, thyroidectomy

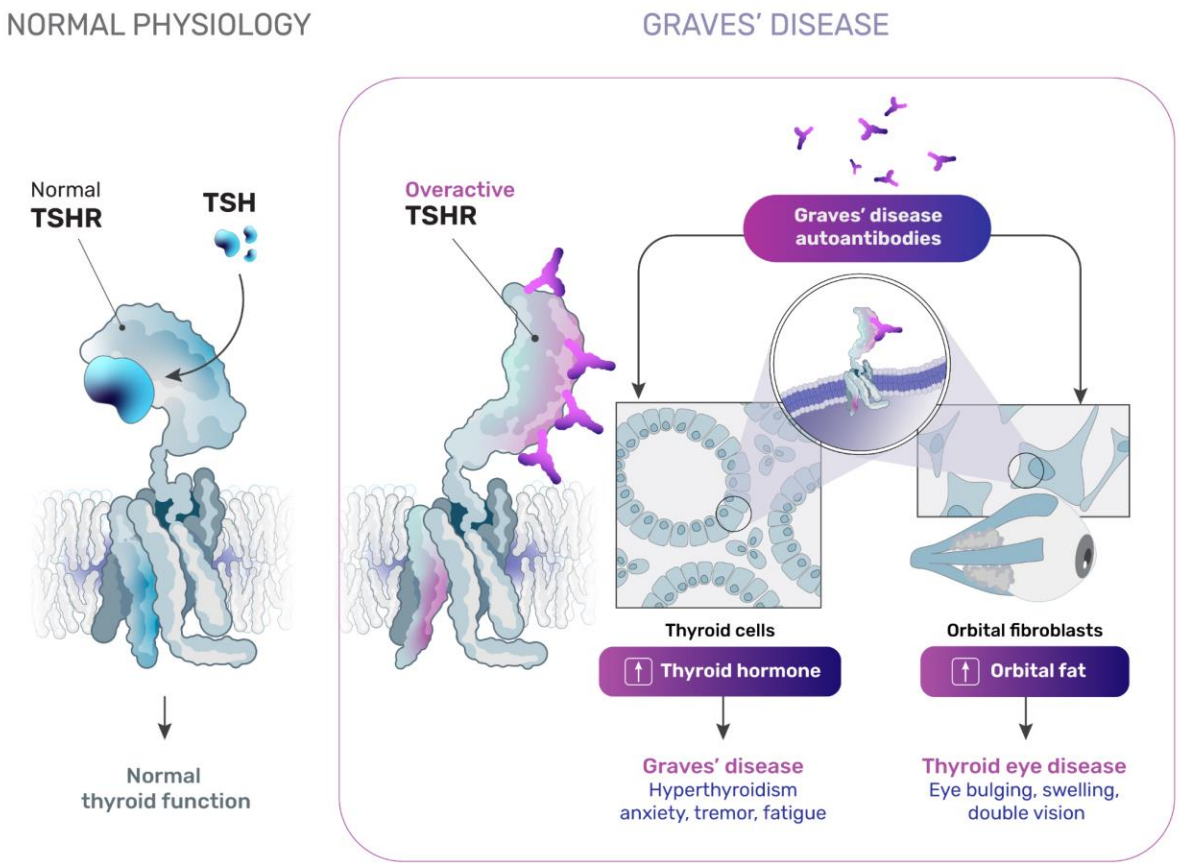
TED

- Develops in ~50% of Graves' disease patients
- TEPEZZA® (anti-IGF-1R) decreases proptosis but requires multiple IV infusions; serious side effects (e.g., hearing loss)

Challenge: Each Patient Has Unique Autoantibodies

- High-affinity, frequently polyclonal, high titer

Our Strategy: TSHR NAM as oral disease-modifying treatment for all Graves' disease and TED patients



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Oral Small Molecule TSHR NAMs Reversed Symptoms in Novel Graves' Disease Model

- **Selective TSHR NAMs**
  - Blocked activation of TSHR by patient-derived autoantibodies
  - Insurmountable NAM profiles in cell-based assays
- **Preclinical Leads Inhibited Diverse Patient Autoantibodies**
  - Fully inhibited several Graves' patient polyclonal serum samples in primary orbital fibroblasts
- **Reversed Graves' Animal Disease Model Effects**
  - Normalization of thyroid hormone T4
  - Reduction in thyroid weight
  - Reversal of proptosis



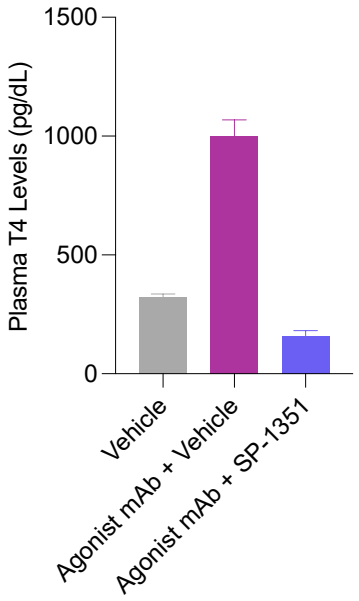
Mouse

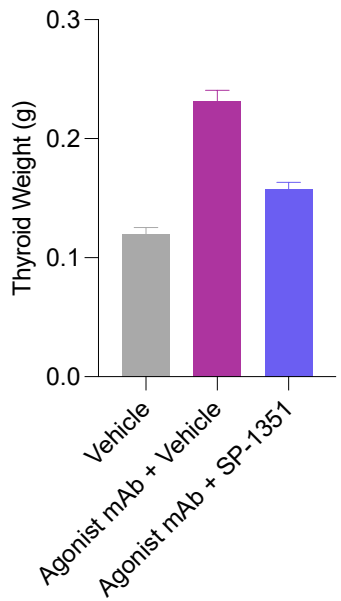
TSHR Activating Antibody → 6 weeks

↑ Thyroid Hormone Levels
↑ Thyroid Size
↑ Eye Proptosis (bulging)

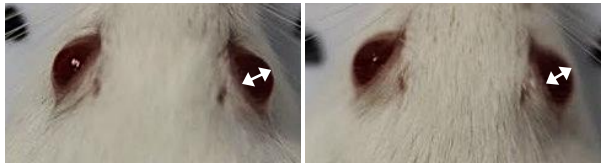
TSHR Activating Ab +TSHR NAM → 1 week

Reversal of Thyroid and Eye Manifestations

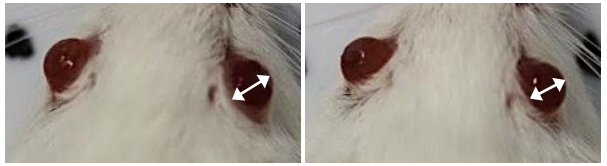




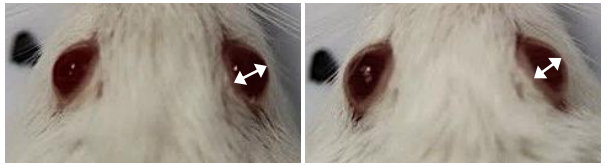
Isotype mAb control + Vehicle



Agonist mAb + Vehicle



Agonist mAb + SP-1351



Lead optimization is ongoing towards selection of a development candidate

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Metabolic Programs

Oral Small Molecule Programs Targeting GLP-1R, GIPR, GCGR and Other Targets for Obesity, Diabetes, and Other Cardiometabolic Diseases

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Collaboration with Novo Nordisk for Oral Small Molecules for Metabolic Diseases

Septerna and Novo commenced four initial R&D programs targeting five GPCRs

- Includes GLP-1, GIP and glucagon receptors
- Collaboration includes Septerna's preclinical, selective, oral, small molecule GIP receptor agonists

Potential multi-billion $ opportunity

- $195M upfront payment received in July '25
- ~$500M in R&D, regulatory and commercial milestones for each program
- Mid-to-high single-digit tiered royalties based on global product sales
- Opt-in right for worldwide profit-share for one program

Novo responsible for coverage of all collaboration R&D expenses



Collaboration Objective: discover, develop and commercialize multiple novel mono-, dual-, or triple-acting oral small molecule drug candidates directed to obesity, type 2 diabetes and other cardiometabolic diseases

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Building a World-Class GPCR-Focused Biotechnology Company

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Proven Leaders in GPCR Drug Development and Company Building

Senior Leadership



Jeff Finer, MD PhD
CEO



Liz Bhatt, MS MBA
President & COO



Gil Labrucherie, CFA JD
CFO



Uwe Klein, PhD
SVP Biological Sciences



Dan Long, DPhil
SVP Drug Discovery



Samira Shaikhly
CPO



Mark Wilson, JD
CLO

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Septerna: Pioneering a New Era of GPCR Drug Discovery

- **Portfolio of oral small molecule GPCR-targeted programs**
- **Multi-product pipeline, each with a multi-billion $ market opportunity**
- **Native Complex Platform® drives rapid compound identification and portfolio expansion**
- **Well-capitalized with cash runway expected to support operating plans at least into 2029**

Wholly-Owned Programs	Development Status			
Program / Target Mode of Action	Discovery	IND-enabling	Phase 1	Phase 2
SEP-479 (PTH1R) Agonist				Anticipate Phase 1 data in Q12027
SEP-631 (MRGPRX2) Negative Allosteric Modulator				
TSHR Program Negative Allosteric Modulator				
PTH1R Program Agonist (for Osteoporosis)				

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

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* Partnership also includes two undisclosed targets



septerna

Pioneering a New Era of GPCR Drug Discovery

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