XXV Encuentro de Cooperación Farma-Biotech

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First-in-class dual-acting analgesics

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UNIVERSITAT DE BARCELONA

Bosch i Gimpera
UNIVERSITAT DE BARCELONA

UNIVERSIDAD DE GRANADA

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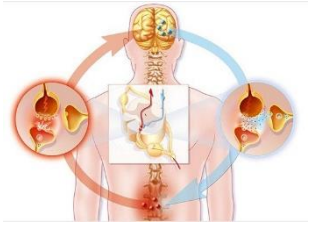
2. The Product- a) Target Indications

1 in 5 suffers from pain



Huge economic costs

Unmet medical, social, and economic **need**

Pain is a multifactorial disease
...and it is an enormous health problem.

Current treatments
- **Limited efficacy** and/or severe **side effects** (opioid epidemic: addition, respiratory depression, constipation…)
- **Not many recent additions**

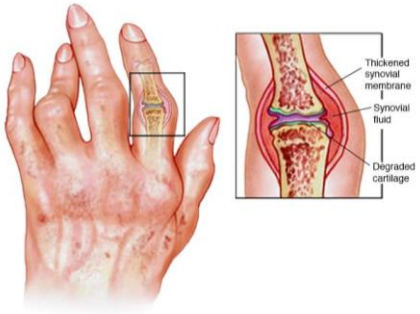
Need for improved drugs tackling more than one mechanism of action

Main indication | **Postoperative pain**

> 300 million people/year undergo **surgery**

> 50% suffering from pain in the immediate postoperative period

Secondary indication | **Rheumatoid arthritis**

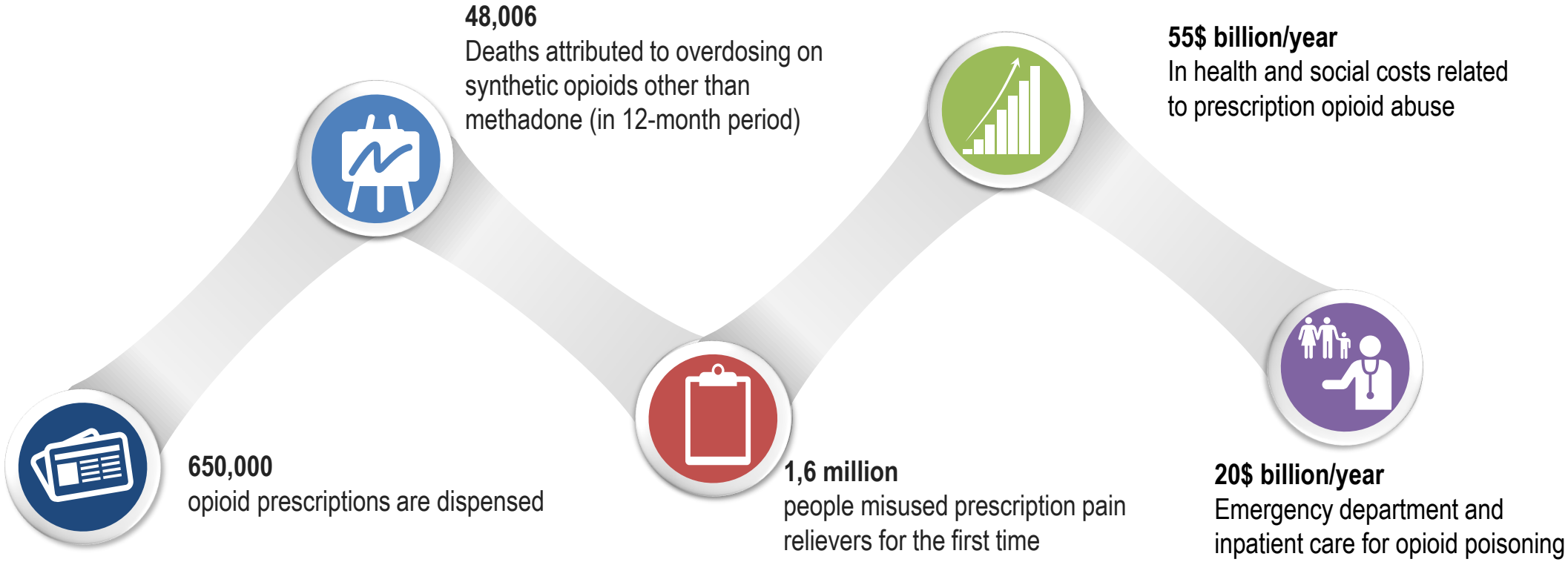


- Very common autoimmune disease - one of the most common causes of chronic pain (0.5-1% of the world population)

- Pain is the most prevalent and disabling symptom for patients with rheumatoid arthritis

2. The Product- a) Target Indications

THE ECONOMIC IMPACT OF EFFECT ADVERSE OF OPIOIDS



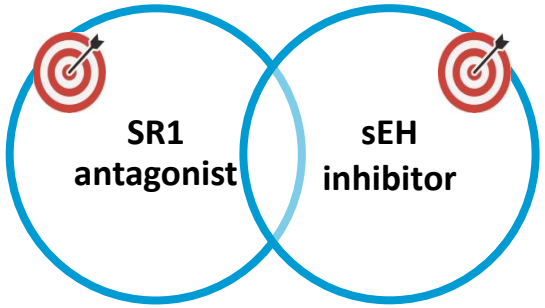
10 million Americans reporting using opioids for non-medical reasons, nearly 2 million meeting substance abuse diagnostic criteria for opioids, and as many as 91 deaths every day due to opioid overdose**, it is imperative that effective methods for opioid-sparing pain control be employed whenever possible**

The impact has been so **great that the National Academies of the USA** has developed a new framework for the revision of criteria **for administration of opioids in all indications in which acute pain is present**

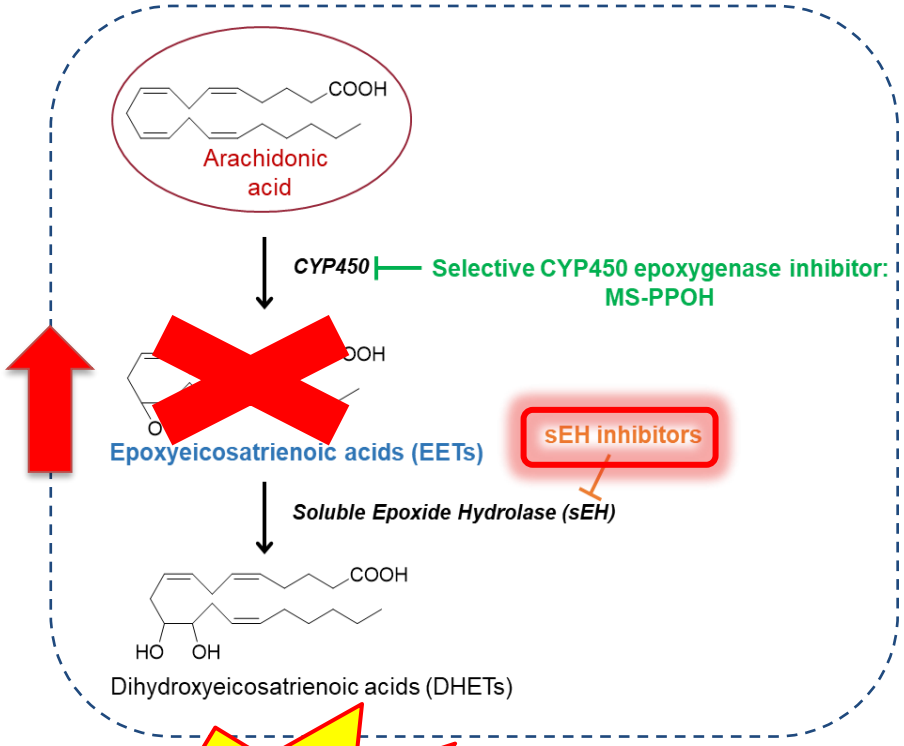
Source: Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence (2020) Committee on Evidence-Based Clinical Practice Guidelines for Prescribing Opioids for Acute Pain. A Consensus Study Report of the Nationall Academies of Sciences, Engineering and Medicine

2. The Product- b) Innovative mechanisms of action

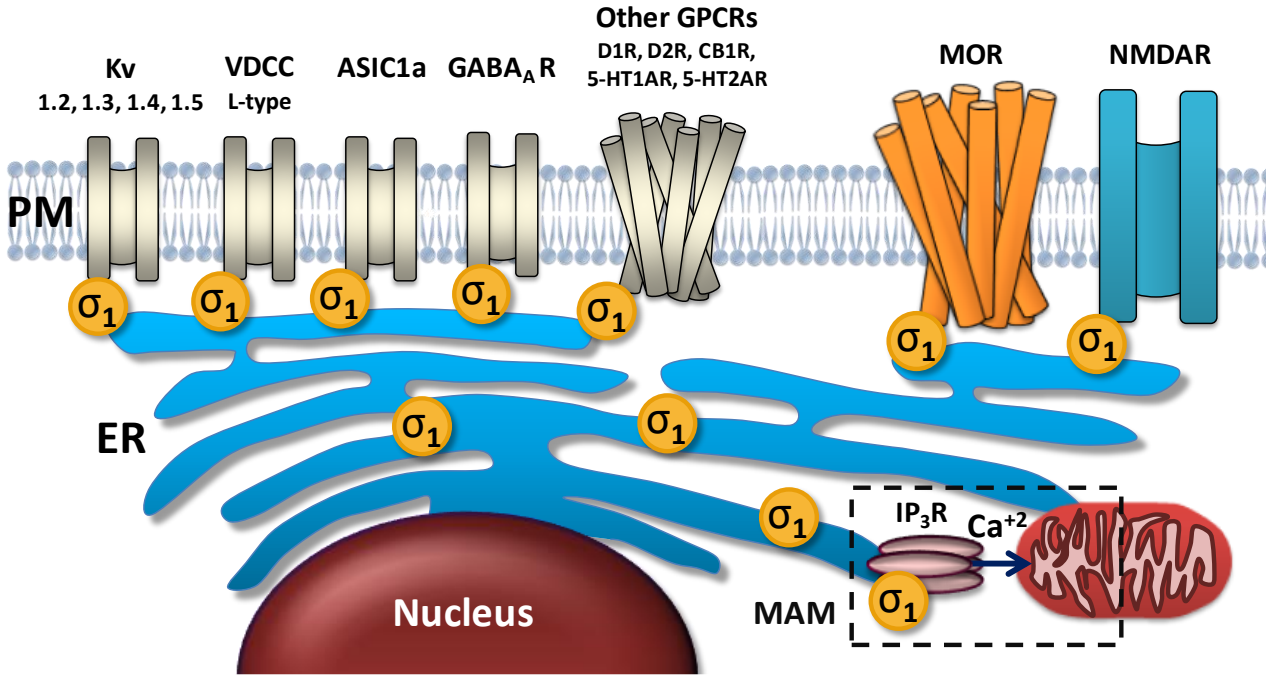
A first-in-class dual acting S1R-sEH molecule



sEH: a promising new target for pain treatment



Sigma-1 receptors: Ca2+-sensing chaperone



Reviewed by Sánchez-Fernández et al., 2017 - in: Sigma Receptors: Their Role in Disease and as Therapeutic Targets S.B. Smith, T.-P. Su (eds.), Springer

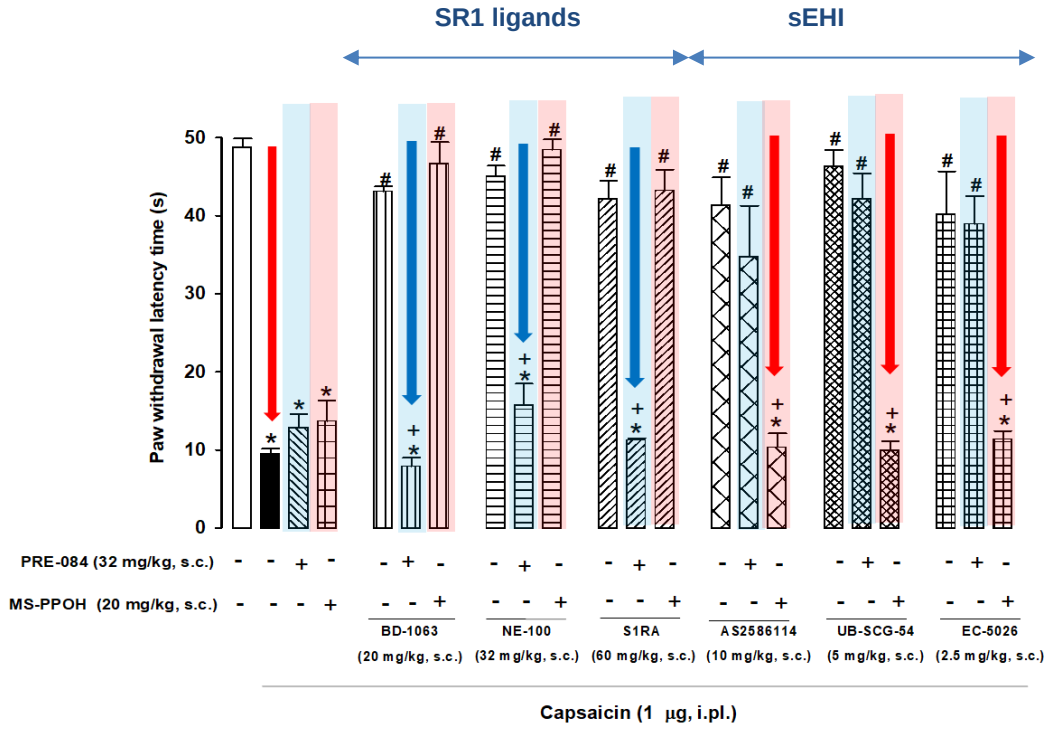
Pain relief

Selective compounds targeting each of these receptors have demonstrated safety in Phase I clinical trials in humans

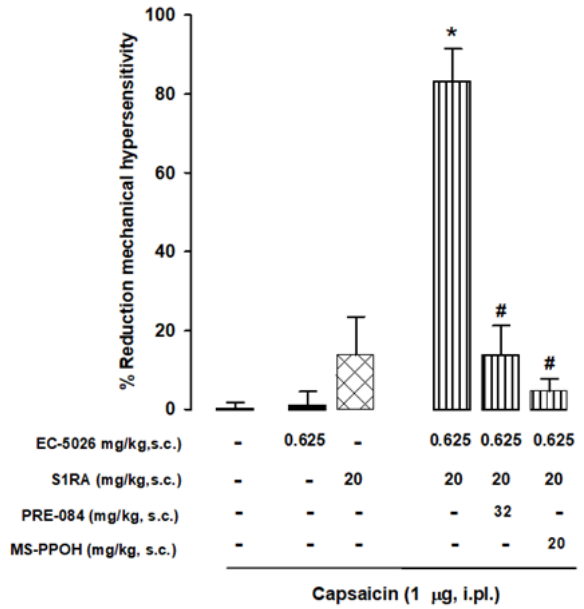
SAFE TARGETS

Modulators of neurotransmission

CAPSAICIN INDUCED MECHANICAL ALLODYNIA: COMPETITION EXPERIMENTS WITH SR1 AND sEHI



Source: Latremolier 2024https://doi.org/



- Activities of different SR1 antagonists are reversed by a SR1 agonist (PRE-084), but not by an inhibitor of the pathway targeted by sEHI (MS-PPOH).
- Activities of different sEHI are reversed by an inhibitor of the pathway targeted by sEHI (MS-PPOH), but not by a SR1 agonist (PRE-084).
- **Low doses of both S1RA and EC5026 show strong synergistic activity**
- **Synergistic activity is reversed by both PRE-084 and MS-PPOH: Both mechanisms are involved**

TO DESIGN AND SYNTHESIZE DUAL-ACTING COMPOUNDS: Ex. UB-EPB-117

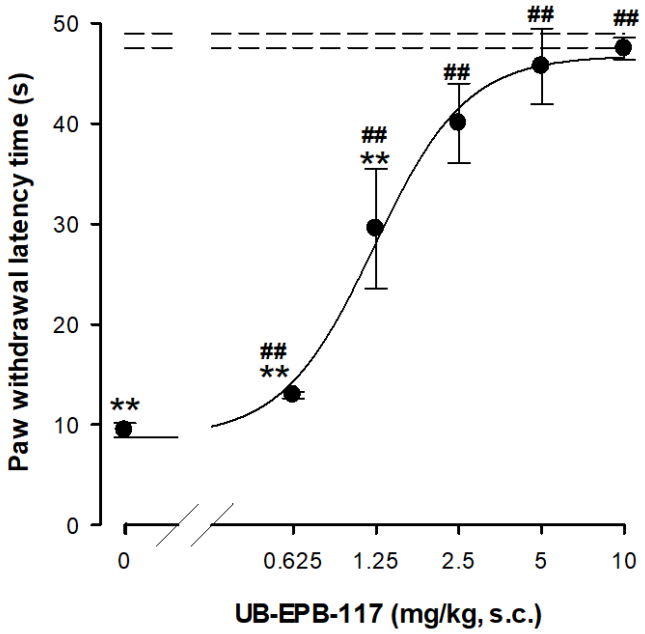
SELECTIVITY OF A REPRESENTATIVE COMPOUND

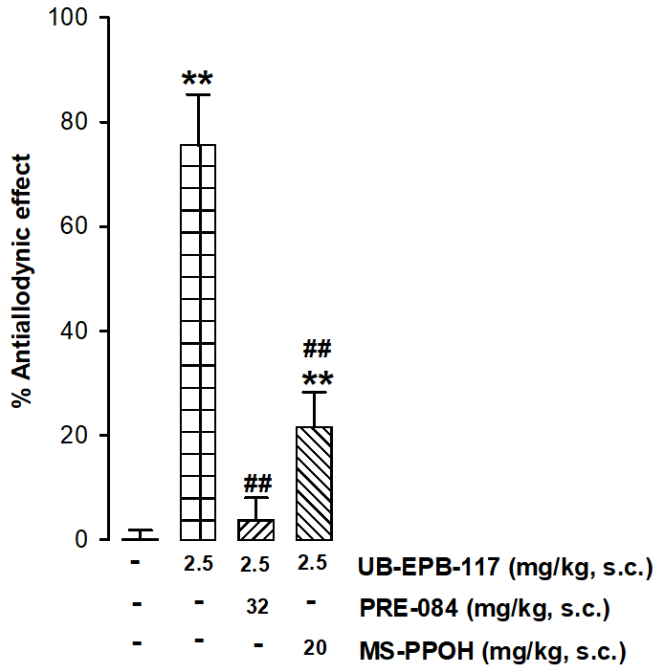
Cpd	UB-EPB-117
hERG channel (% inhibition at 10 µM)	18
Kinase (scanEDGE Eurofins panel)	No inhibition of 97 kinases at 1 µM
Selectivity (Eurofins)	K_i > 10 µM against 55 receptors, channels (eg., CB1, CB2, DOP, KOP, MOR, etc.)
Selectivity (USC)	h5-HT_{2A}, K_i = 8.6 µM hα_{1A}, K_i = 4.5 µM
Selectivity (Eurofins)	IC_{50} > 10 µM against 7 enzymes (eg. COX1, COX2, LOX, AChE, etc.)

- **Compounds with a very high selectivity** with regards to kinase, and the Eurofins 55 receptor and channel safety panels
- **Low hERG inhibition** under standard conditions

CAPSAICIN INDUCED MECHANICAL ALLODYNIA:

ACTIVITY OF REPRESENTATIVE DUAL INHIBITOR

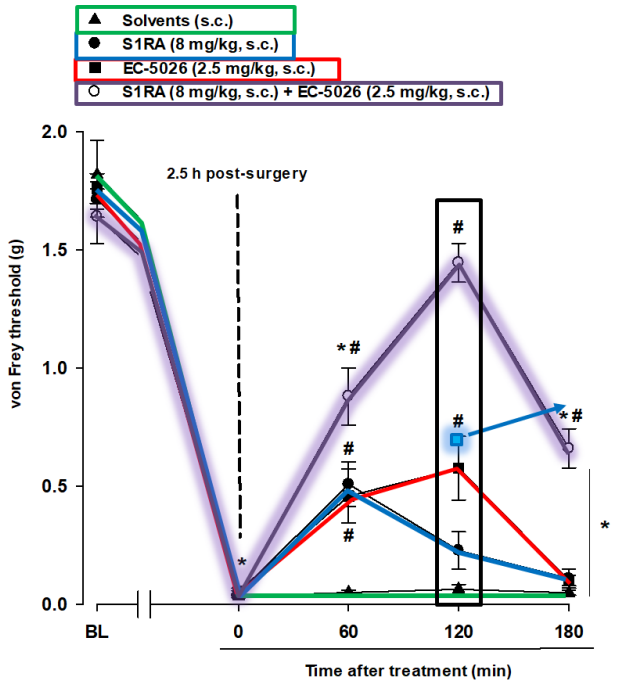




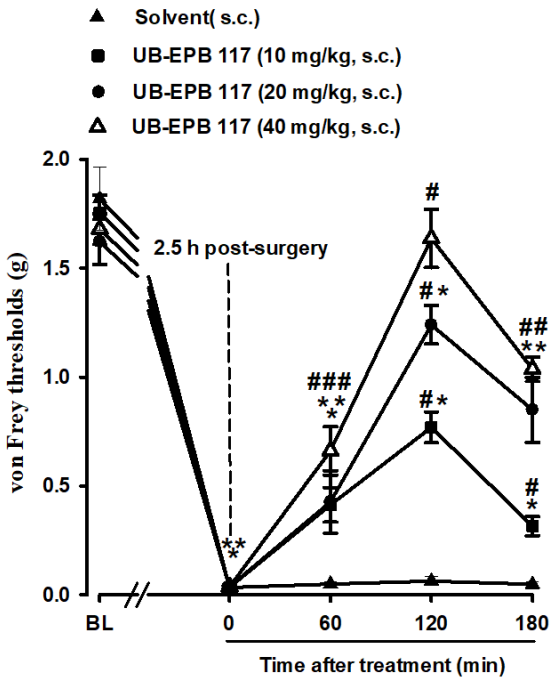
- **Selected dual inhibitors showed potent antialllodynic activity**
- Both mechanisms are **working synergistically** using a single molecule

POST-OPERATIVE PAIN: SELECTED COMPOUND

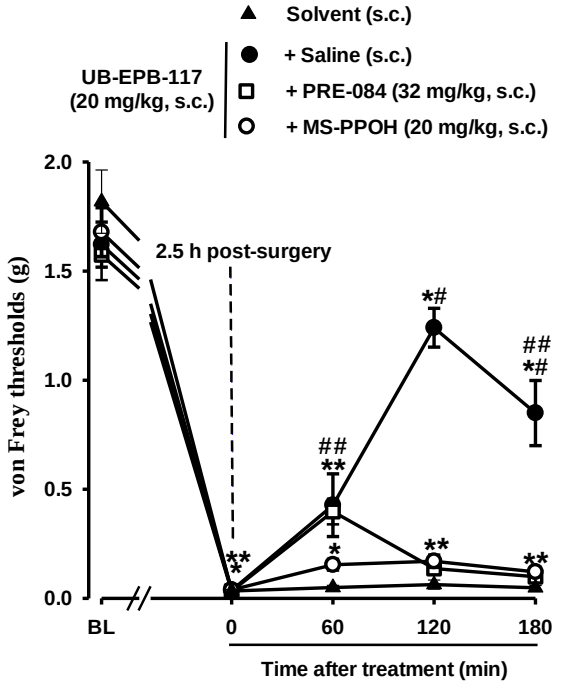
Co-administration of SR1 antagonists and sEHI



Dual selected compound

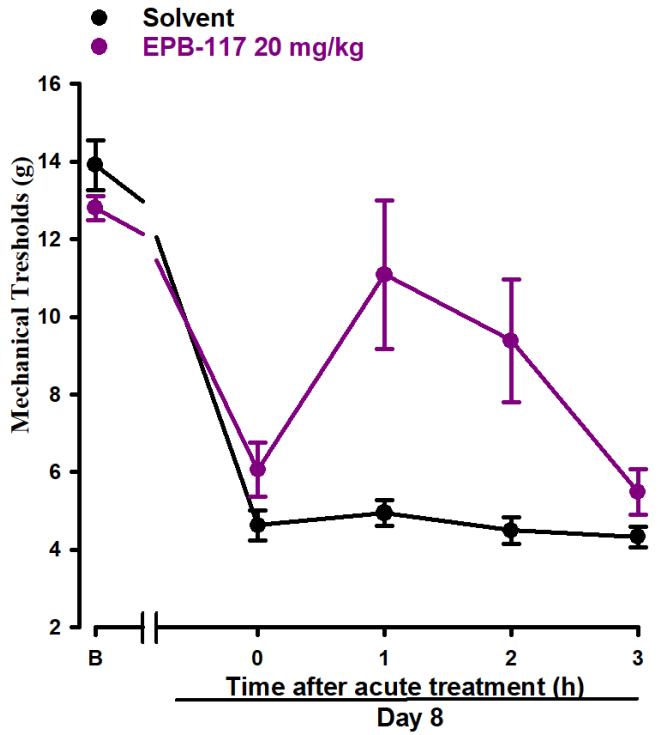


Competition experiments



- **SR1 antagonists and sEHI show synergistic activity**
- Selected compounds (dual inhibitors) show **potent analgesic activity**
- Activity of the selected compound is significantly reduced by both the σ1 receptor agonist PRE-084 and the sEH pathway inhibitor MS-PPOH: **indicating a dual mechanism as a σ1 antagonist and sEH inhibitor**

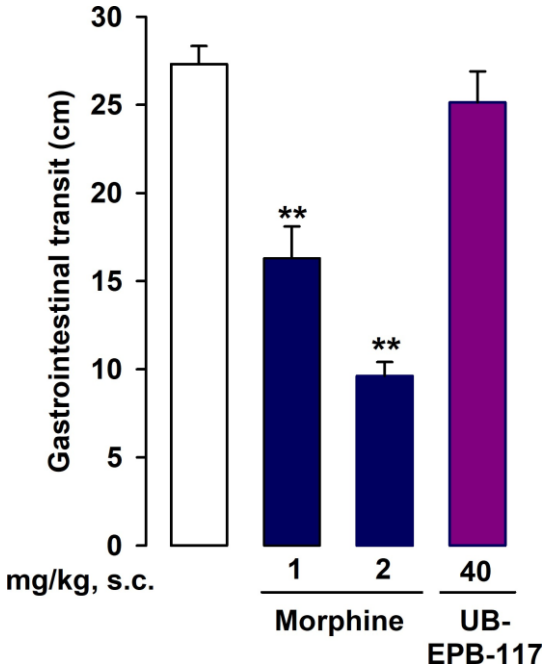
PAIN IN COLLAGEN INDUCED ARTHRITIS: SELECTED COMPOUND



- Selected compounds showed activity in pain caused collagen induced arthritis

EFFECT ON GASTROINTESTINAL TRACT OF SELECTED COMPOUNDS

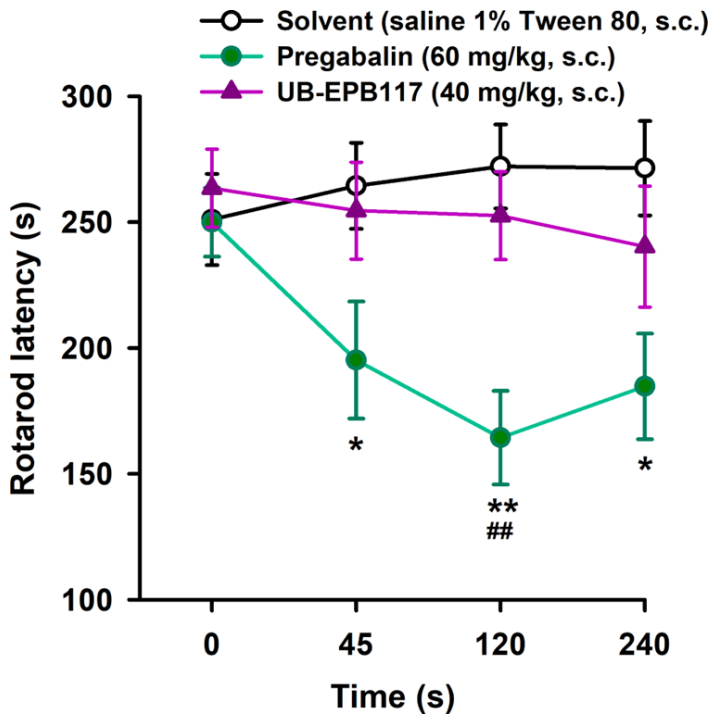
Mice model 40mg/kg s.c,



- **Morphine induces constipation** in a dose dependent manner
- Selected compounds d**o not induce any constipation**

EFFECT ON SEDATION AND MOTOR ACTIVITY OF SELECTED COMPOUNDS

Mice model 40mg/kg s.c,



- **Pregabalin induced a significant sedation** as measured by **reduction of motor activity**.
- Selected compounds **do not induce sedation or affect motor activity**

2. The Product- c) Differential features facing the market

Differentiated positioning of DUALES (dual S1R-sEHI molecule)

Novel Mechanism of Action (MoA):

- **Dual inhibitor S1R (Sigma-1 receptor) + sEHI (soluble epoxide hydrolase inhibitor)** → **first-in-class** (no marketed products or pipeline competitors with this combination).
- **Non-opioid** → **avoids abuse/addiction risk** → strongly aligned with **post-opioid crisis market demand**.
- Potential **opioid-sparing effect** → reduces opioid consumption post-surgery, one of the **key unmet needs** in the market.

Clinical value:

- **Potentially improved safety profile** vs opioids and NSAIDs.
- Potential for **combination use** with other analgesics → flexibility in multimodal pain management

Competitor comparison (marketed & pipeline)

Current competition (marketed drugs):

- **Top 10 sales dominated by opioids & NSAIDs** → mature markets, largely generic → **low prices**.
- Key products:
  - **Exparel (liposomal bupivacaine)** → ~$0.5 B sales.
  - **Celecoxib (Celebrex)**.
  - **Zynrelef (bupivacaine + meloxicam ER)**.

Pipeline competition:

- Most drugs are still in **Phase I**.
- Most frequent MoA: **receptor agonists** and **simple enzyme inhibitors**.
- Notable emerging competitors:
  - **VVZ-149 (Vivozon)** → non-narcotic, comparable to morphine.
  - **VX-548 (Suzetrigine, NaV1.8 inhibitor)** → most advanced direct competitor (NDA approved)

2. The Product- c) Competitive positioning summary

Key aspect	DUALES (S1R-sEHI dual)	Current competitors	Relevant pipeline
MoA	Dual (first-in-class) → S1R + sEHI	Monotherapy (opioid, NSAID, anesthetic)	Some novel MoA (VVZ-149, VX-548)
Opioid-sparing	✔	Partial or no	Some candidates
Duration of action	Long	Limited in many cases	Variable
Safety profile	Improved (non-opioid, fewer adverse events)	High opioid risk, NSAIDs with GI/cardiovascular risks	Variable
Level of innovation	**Very high** (first-in-class dual)	Low-moderate	High in some cases
Development stage	Preclinical / early (validated MoA in models)	Marketed	Phase I–III
Premium pricing opportunity	**High** (novel MoA + clear unmet needs)	Low (commoditized)	Medium
Combination potential with other Rx	✔	Partial	Variable

2. The Product- c) Value Proposition

Feature	Market Advantage / Value Proposition
Dual action — synergistic efficacy	Combined S1R antagonism + sEH inhibition targets both neuropathic and inflammatory pain mechanisms simultaneously, delivering superior pain relief versus single-target agents.
Reduced dosing requirements	Potent synergy enables **lower effective doses**, minimizing drug exposure and reducing potential adverse effects.
Lower incidence of adverse effects	Non-opioid mechanism avoids sedation, respiratory depression, tolerance, dependence, and constipation common to opioids.
Extended duration of action	Enables **once-daily oral dosing**, improving **patient adherence** and supporting use in both acute and chronic pain indications.
First-line potential in postoperative pain	Ability to **reduce or eliminate opioid need** in postoperative care, supporting opioid-sparing hospital protocols and payer initiatives.
Easier reimbursement & faster clinical adoption	Non-opioid profile aligns with payer and HTA (Health Technology Assessment) priorities, facilitating reimbursement approval and clinician adoption.
Broad market expansion potential	Initial focus on **postoperative pain**, with clear path to **chronic pain markets** (e.g. rheumatoid arthritis, osteoarthritis, neuropathic pain).
Scalable, cost-effective manufacturing	Oral small molecule — cost-efficient and scalable versus biologics or devices, supporting global commercial rollout.
Strong IP position	Robust patent coverage offers **long exclusivity window**, enhances partner ROI, and deters competitive entry.

2. The Product- d) Current status of development

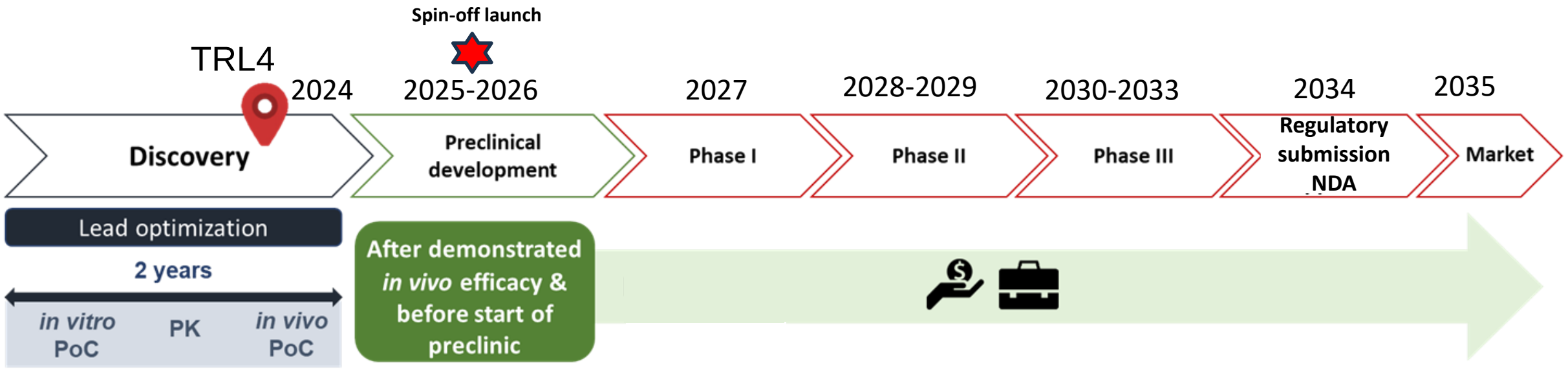
The proposed first clinical indication is **postoperative pain following bunionectomy**. This surgical procedure presents a high prevalence and facilitates **efficient patient recruitment**, providing an optimal pathway for initial clinical development.

Additional potential indications under consideration include:
- **Chronic pain associated with rheumatoid arthritis**.
- **Postoperative pain following hip or knee replacement surgeries**.

The development plan envisions progression through:

1. **Completion of preclinical safety studies**.
2. **Regulatory submission for first-in-human (FIH) clinical trials**.
3. **Phase I trials** to establish safety and pharmacokinetics in healthy volunteers.
4. **Phase II proof-of-concept trials** in patients undergoing bunionectomy.
5. **Expansion to broader indications** based on clinical results and regulatory guidance.

2. The Product- d) Current status of development



- The company's primary objective is to achieve **clinical proof-of-concept by 2028**, which will serve as a key inflection point to unlock **strategic partnerships or out-licensing opportunities**.
- Given its **differentiated, non-opioid mechanism of action**, and the scalability of **small-molecule manufacturing**, the program is well-positioned to establish a **first-in-class alternative** in the treatment of **postoperative pain** and **chronic pain conditions**.
- **Current Stage: Late-stage discovery and Preclinical Validation**

•Successful preclinical validation in **animal models (mice and rats)**.
•Chemical optimization and **good pharmacokinetic profile** (DMPK).
•Upcoming stages: oral efficacy evaluation and assessment of specific side effects (addiction, tolerance).

2. The Product- d) Current status of development

The lead candidate has been selected, and IND-enabling studies are underway.

➢ Activities include:

- GLP toxicology
- Safety pharmacology
- Drug formulation development
- CMC scale-up for clinical trial API (active pharmaceutical ingredient)

Concept	Cost	Concept	Cost
CMC		chromosomal aberration	9.000,00
API Scale-up and manufacturing of GMP-like	550.000,00	hERG	18.000,00
Formulation development	100.000,00	Rat respiratory	20.000,00
Discovery		rat FOB	15.000,00
Lead optimisation	500.000,00	CV safety dog telemetry	70.000,00
Safety Pharmacology		**Toxicokinetics**	
Inmmunogenicity	50.000,00	Rat MTD	25.000,00
In vitro ADMET Tox	25.000,00	Dog MTD	55.000,00
Express selectivity panel (CEREP)	6.000,00	Rat 28 day tox	72.000,00
Toxicity and in vitro PK (CEREP)	7.000,00	Dog 28 day tox	200.000,00
In vivo efficacy (Crown Bio and Charles River)	50.000,00	**Clinical development**	
Regulatory Pharmacology (Eurofins Advinus)	20.000,00	Phase I	1.000.000,00
Microbiology off target panel	18.000,00	**Total preclinical development**	1.830.000,00
Micronucleus	3.000,00	**Total Clinical development**	1.000.000,00
AMES	17.000,00	**Total development plan**	**2.830.000,00**

2. The Product- d) IPR protection

- **PATENT FAMILY 1:** PCT/EP2023/082202. International publication number: WO2024/105234 A1. DUAL INHIBITORS OF SIGMA-1 RECEPTOR AND SOLUBLE EPOXIDE HYDROLASE AND THEIR USE IN THE TREATMENT OF PAIN. Priority date: 18/Nov/2022. Currently in the process of being extended to the following territories: US, CA, IN, AU, JP, KR, CN and EP.
- **PATENT FAMILY 2:** PCT/EP2025/060895. COMPOUNDS CAPABLE OF ACTING ON S1R AS WELL AS ON sEH AND USES THEREOF. Priority date: 23/Apr/2024.
- **SYNERGIA PATENT:** PCT/EP2023/082181: SYNERGISTIC COMBINATIONS OF A SIGMA RECEPTOR 1 (S1R) ANTAGONIST AND A SOLUBLE EPOXIDE HYDROLASE INHIBITOR (sEHI) AND THEIR USE IN THE TREATMENT OF PAIN. Priority date: 17/Nov/2023.

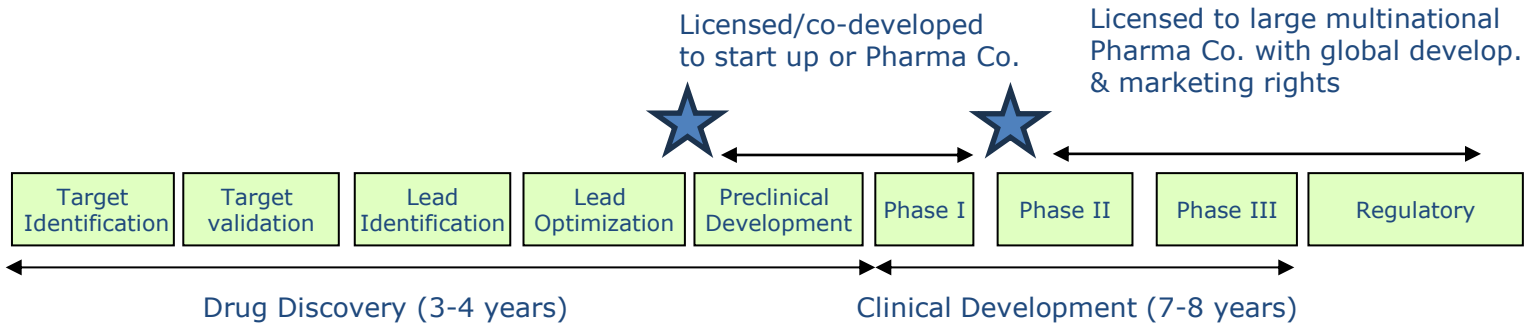
What does the IP contribute to investors and partners?

- **Barrier to entry**: The **novel chemical entities (NCEs)** protected by the patents give the project a **strong freedom to operate** and **prevent fast followers** from copying the dual mechanism.
- **Exclusivity window**: The patents (2023/2025 filings) ensure a **multi-year exclusivity window**, which allows any commercial partner to enjoy **market exclusivity** — critical for **pricing and reimbursement** negotiations.
- **Licensing leverage**: Strong IP enables the project to negotiate **better licensing terms** (higher upfronts, milestones, royalties) with pharma companies.
- **Asset valuation**: For VCs, strong IP **de-risks the investment** and increases the **potential valuation** of the spin-off or asset in future financing rounds or M&A.
- **Platform potential**: Since the IP covers a **family of molecules**, it opens opportunities to develop **second-generation compounds** or explore **additional indications** — increasing **pipeline value** for partners/investors.

2. The Product- f) Pitfalls & Risks to be considered

Risk Category	Description	Mitigation Strategy
Translational Risk	Preclinical efficacy may not fully translate to human clinical outcomes in terms of efficacy or tolerability.	Design robust translational models; early biomarker strategy; adaptive trial designs.
Regulatory Risk	Navigating regulatory pathways for this novel dual mechanism of action may present unforeseen challenges.	Early and continuous engagement with FDA and EMA; seek scientific advice; align on regulatory expectations.
Safety Profile Uncertainty	Comprehensive chronic toxicity, CNS-related safety (cognitive effects), and potential off-target effects need characterization.	Rigorous IND-enabling toxicology studies; CNS-focused safety panels; staged clinical development.
Clinical Trial Execution Risk	Challenges in patient recruitment and retention in postoperative pain trials; evolving pain management protocols.	Site pre-selection with high recruitment potential; patient engagement strategies; adaptive protocols.
Manufacturing and CMC Risks	Optimization of oral bioavailability and ensuring batch-to-batch consistency is required.	Early CMC planning; scalable GMP manufacturing processes; formulation optimization workstreams.
IP Landscape	Vigilance needed to monitor competing IP and maintain freedom-to-operate in dual-acting agents and emerging competitors.	Conduct regular FTO (Freedom to Operate) reviews; collaborate with IP counsel; proactive IP strategy.
Competitive Dynamics	Rapid evolution of the pain management market with new entrants (biologics, devices, non-opioid molecules).	Maintain differentiation focus; continuous competitive intelligence; partnership discussions to accelerate development.
Financing Risk	Ongoing funding required to advance to clinical proof-of-concept amid a volatile biotech VC environment.	Diversified funding strategy: non-dilutive grants + staged VC rounds; maintain strong investor relations.

3. Partnering Opportunities



We offers multiple partnering pathways:

- **Strategic co-development alliances** with pharmaceutical companies focused on **pain management** or **non-opioid analgesics**.
- **Licensing agreements** for regional or global rights, post-Phase I or post-proof-of-concept milestones.
- Potential **joint venture or spin-off structure** to advance clinical development.

Key differentiators attractive to potential partners:

- **First-in-class dual mechanism** addressing a major unmet need in **postoperative and chronic pain**.
- **Non-opioid profile** aligned with current global efforts to reduce opioid dependency.
- **Favorable manufacturing scalability** (small molecule oral therapy).
- Clear **regulatory interest**, potential for **Fast Track / Breakthrough Designation**.

Partner value proposition:

- Opportunity to **lead the non-opioid pain market** with an innovative therapy.
- Entry into a market segment with **multi-billion dollar potential**.
- Potential to expand indications beyond initial **postoperative pain** to **rheumatoid arthritis** and broader **chronic pain** markets.

Thank you for your attention.

We look forward to exploring **potential collaborations** and **partnership opportunities** with you.

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