Profile of Three Drugs that Could Change the Profile of Pain Medicine

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Raymond W. Houde Lectureship Award, Eastern Pain Association, December 3, 2022

Financial Disclosures

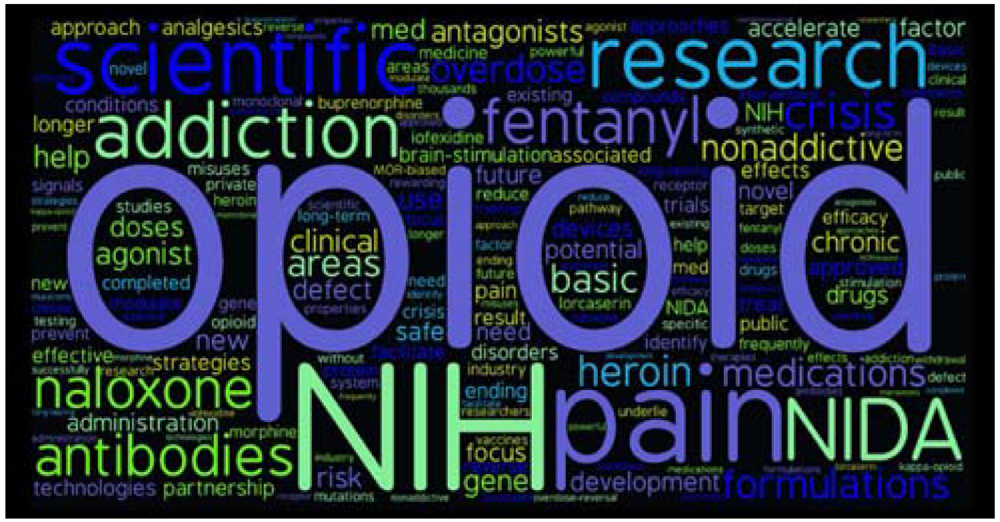
Dr. Schmidt is a part-time employee or consultant to three companies that have clinical-stage analgesic products in Phase 1 through Phase 3 development that will be discussed in this presentation:

- Ensysce Biosciences, La Jolla, California
- EicOsis Human Health, Davis, California
- Helixmith Co., Ltd, Seoul, South Korea, and San Diego, California

Ensysce Biosciences and EicOsis Human Health have received funding from the National Institutes of Health HEAL Initiative (NINDS and NIDA). Additional funding has been provided by shareholders of each company.

Pain in the News:

Public-Private Initiative to Address the Opioid Crisis



Opioid misuse and addiction is an ongoing and rapidly evolving public health crisis. Millions of Americans suffer from opioid use disorder, and millions more suffer from chronic pain. The urgency and scale of this crisis calls for innovative scientific solutions. As part of a government-wide effort to address this crisis, NIH is supplementing existing research efforts with a public-private collaborative research initiative on pain and opioid abuse. In April 2017, NIH Director Francis S. Collins, M.D., Ph.D., met with research and development leaders from the world's leading biopharmaceutical companies to discuss new ways for government and industry to work together to address the opioid crisis. The initial plan for this initiative was recently laid out by Dr. Collins and National Institute on Drug Abuse Director Nora D. Volkow, M.D., in the *New England Journal of Medicine*.

Developing Novel Analgesics is Hard Work!

ANESTHESIOLOGY

Estimates of Probabilities of Successful Development of Pain Medications: An Analysis of Pharmaceutical Clinical Development Programs from 2000 to 2020

Dermot P. Maher, M.D., M.S., M.H.S., Chi Heem Wong, Ph.D., Kien Wei Siah, Ph.D., Andrew W. Lo, Ph.D.

ANESTHESIOLOGY 2022; 137:243–51

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Despite the prevalence and societal costs of pain in the United States, investment in pain medication development is low, due in part to poor understanding of the probability of successful development of such medications

What This Article Tells Us That Is New

- This study examined outcomes and parameters of 469 pain pharmaceutical development programs of 399 unique active pharmaceutical ingredients between 2000 and 2020
- Development of new medications with high abuse potential decreased since the peak of the opioid epidemic, while development programs for low abuse potential medications increased
- The probability of successful development programs was 27.8% for high abuse potential compounds and 4.7% for low abuse potential compounds
- The probability of successful development of a treatment for nociceptive pain was 13.3%, and that for a treatment of neuropathic pain was 7.1%
- Development of pain medications in large phase 3 safety and efficacy trials took an average of 30 months

What's in the Pipeline (??)

Aligning New Approaches to Accelerate the Development of Non-opioid Analgesic Therapies

Christine N. Sang [1] · William K. Schmidt [2]

Accepted: 21 September 2020

Neurotherapeutics
https://doi.org/10.1007/s13311-020-00935-1

What's in the Pipeline (??)

C.N. Sang, W.K. Schmidt

Table 1 Summary of analgesic drugs in development by therapeutic target (December 31, 2019)

Therapeutic target	Phase 1	Phase 2	Phase 3	NDA/BLA submitted	NDA/BLA approved	Recently discontinued
α2δ-1		1	1			
5-HT_2 antagonist		1				
$Alpha_2$ agonist		1				
AMPA glutamate		1				
COMBINATION products	2	8	5	3		2
BIOLOGICS*	15	23	13		2	8
Bisphosphonate			2			1
Cannabinoid (CB1, CB2)	3	2				
Ion channel: calcium (CaV channel)			1			
Ion channel: sodium (NaV channel)		2				1
Ion channel: potassium (KV channel)		1				
CCR2 cytokine antagonist	1					
CGRP antagonist		2	1	2	3	
Corticosteroid			4			
Opioid: mu agonist	3		5	3		7
Opioid: kappa agonist			1			
Opioid: delta agonist	1					
Opioid: endomorphin	1					
Opioid: enkephalinase inhibitor	1					
Opioid: other (NOP, undisclosed)		1	1			
Opioid: prodrug	2					2
GnRH antagonist			1			
Ergot alkaloid			2			
Imidazoline agonist (I2)		1				
JAK1, pan-JAK inhibitor		1		1	1	
Local anesthetic	2	2	1	1		
Neurostimulation		2	1			
NGF inhibitor			2			
NMDA antagonist		2				1
NSAID (COX-1, COX-2)	2	2	1	1		
PDE9 inhibitor		1				
Prostaglandin synthase inhibitor						
Sigma channel blocker		1				
Soluble epoxide hydrolase (sEH) inhibitor	1					
Soluble guanylate cyclase (sGC)		1				
Somatostatin SSTR4 agonist	1					
Superoxide dismutase mimic		1				
Syk inhibitor		1				
Triptan		1		1		
TrkA inhibitor	1	1				1
TRPA1 antagonist		1				
TRPV1 agonist (capsaicin, resiniferatoxin)	1	2	1			
Wnt inhibitor			1			
Other mechanisms of action	6	9	3		2	4
Total	43	72	47	12	8	27

Totals: 43 72 47 12 8 27

Table 1 presents a summary of 214 tracked compounds in development (as of December 31, 2019) that we have been following for the past 3 years; Table 2 presents the data by primary indication. The tables are extracted from a larger database that is available for download on www.paintrials.org/analgdrugdevt. All of the entries are based on publicly available data that are referenced by hyperlinks within the table.

These include 179 compounds in active clinical development, 8 compounds that were recently approved (2018), and 27 compounds that were discontinued or where no development has been reported for extended periods

FDA Approved Analgesics & Related Products (Sep. 2020 to Oct. 2021)

	SPONSOR	BRAND (Generic Name)	INDICATION / FEATURES	DATE
1	Durect	POSIMIR (bupivacaine ER in sucrose-based biodegradable matrix)	“Administration into the subacromial space under direct arthroscopic visualization to produce postsurgical analgesia for up to 72 hours following arthroscopic subacromial decompression”	2/1/2021
2	Heron Therapeutics	ZYNRELEF (bupivacaine + meloxicam co-polymer)	“Soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy and total knee arthroplasty.”	5/12/2021

4 Drug Approvals + 1 Device Approval in 2020-2021 (despite the pandemic)

FDA Approved Analgesics & Related Products (Sep. 2020 to Oct. 2021)

	SPONSOR	BRAND (Generic Name)	INDICATION / FEATURES	DATE
3	Cara Therapeutics	KORSUVA (difelikefalin acetate, peripheral kappa receptor agonist)	“Treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP)”	8/23/2021
4	Esteve Pharmaceuticals	SEGLENTIS (celecoxib + tramadol)	“For acute pain management in individuals with pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate"	10/15/2021

Device	AppliedVR	EaseVRx (Virtual Reality medical device	“As an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction”	6/30/2020

FDA Approved Analgesics & Related Products (Oct. 2021 to Nov. 2022)

	SPONSOR	BRAND (Generic Name)	INDICATION / FEATURES	DATE
1	Zoetis (Animal Health)	SOLENSIA (frunevetmab); felinized injectable anti-NGF mAb	Feline osteoarthritis pain	1/13/2022
2	Elanco US (Animal Health)	ZORBIUM (topical transdermal buprenorphine)	Control of post-surgical pain in cats	1/20/2022
3	Purdue Pharma	Nalmefene HCl Injection (aNDA to REVEX, discontinued in 2008)	Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.	2/8/2022

No Analgesic Drug Approvals in 2020-2021

Opioid Analgesic 4.0. Is it possible?

GEN 1

Tinctures and potions

GEN 2

Pharmaceuticals

Immediate release opioids

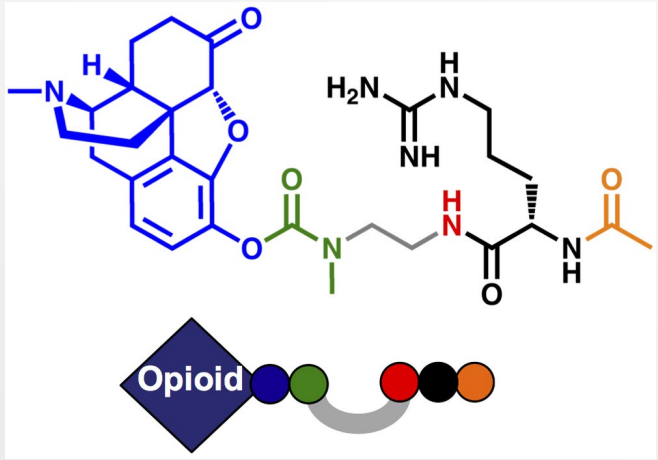
GEN 3

Abuse Deterrent Formulations

Physical formulation approach
ER release to reduce abuse

Next GEN 4.0

TAAP and MPAR™



Chemical modification with 2 step activation

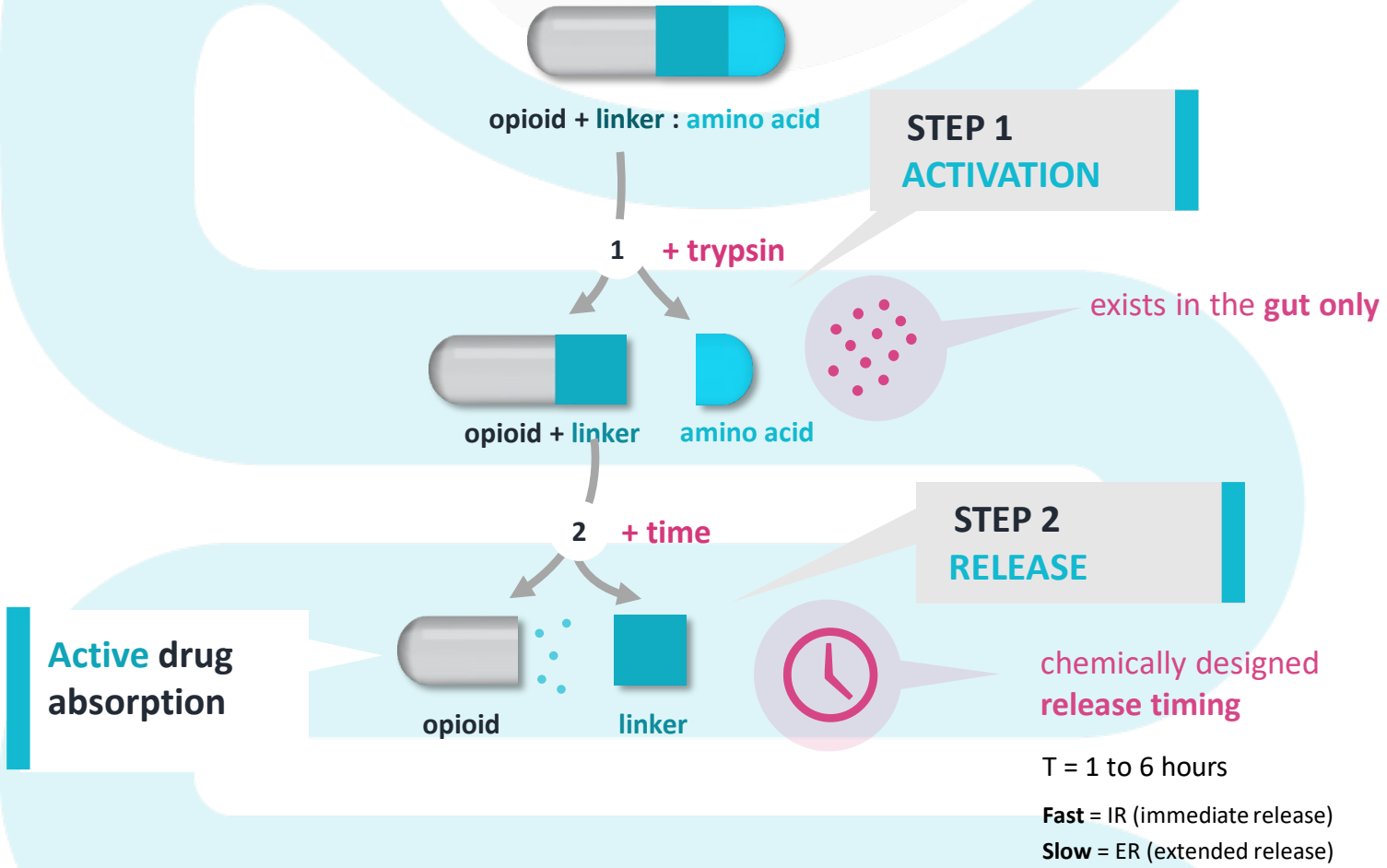
TAAP - Trypsin Activated Abuse Protection

Two-Step Release Process

Chemical modification

Only activated by trypsin

Not altered by manipulation



Protects from:

Chewing

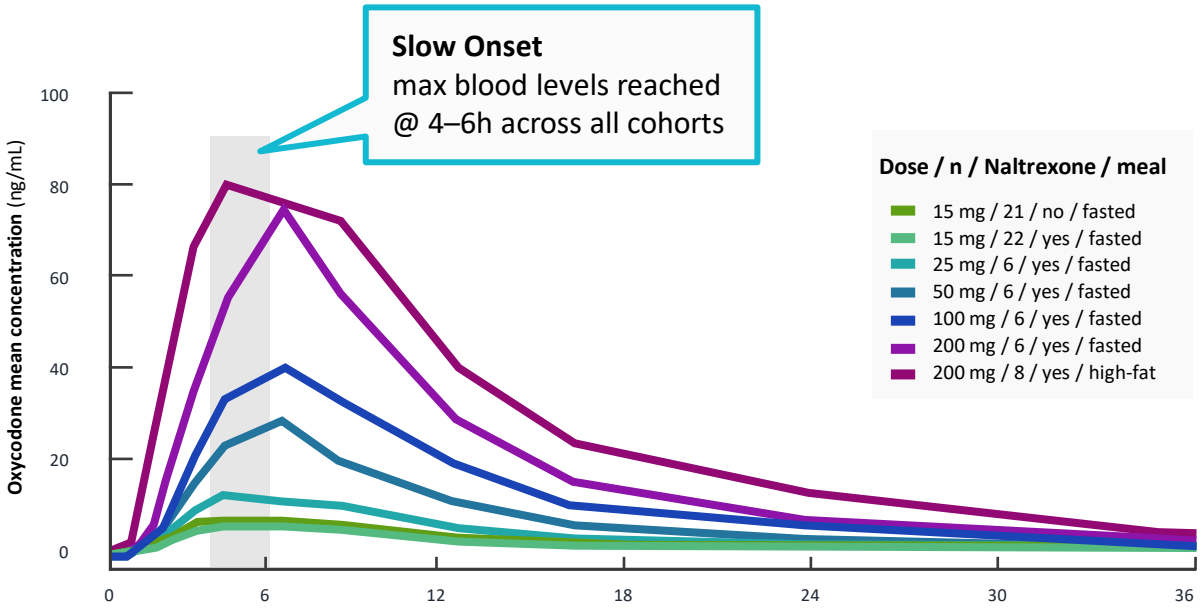
Crushing and snorting

Crushing and injecting

PF614-101

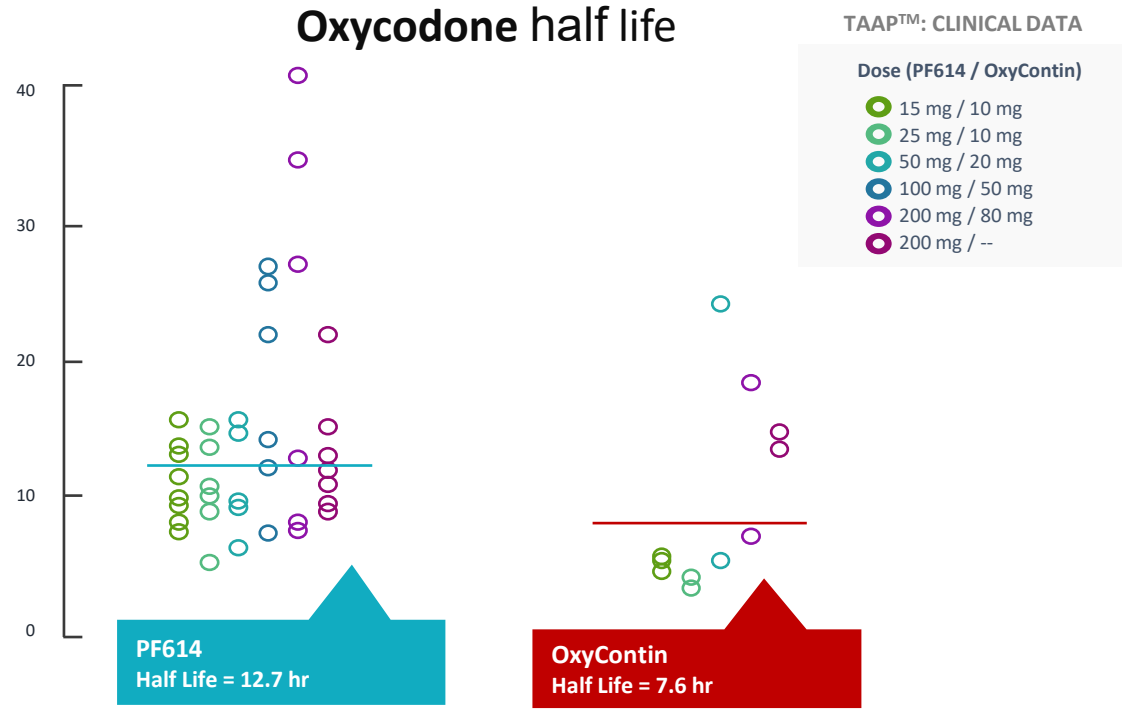
Designed for Safer, More Efficient & Longer-Lasting Pain Relief

Oxycodone Concentration in Blood vs. Time following **PF614** administered **as** oral solution



TAAP: HUMAN CLINICAL DATA

Oxycodone half life



PF614 provides slow onset, good safety profile, efficient conversion to oxycodone and longer half-life than OxyContin.

MPAR™ Multi-Pill Abuse Resistance

Combination Product With Dose-Triggered Trypsin Inhibition

MPAR™ Combination Product Legend:

TAAP–enabled opioid | Trypsin Inhibitor

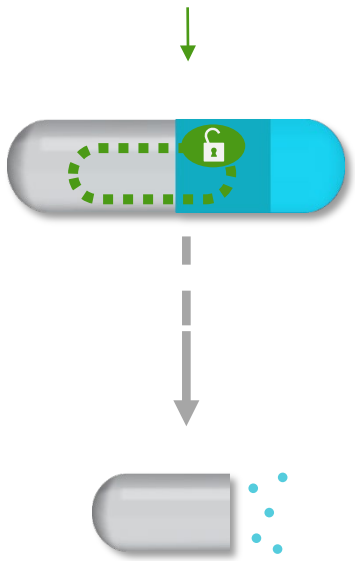
PRESCRIBED DOSE

No Interference when **normal** dose taken; **Low dose of trypsin inhibitor (nafamostat)** does not affect release of the opioid

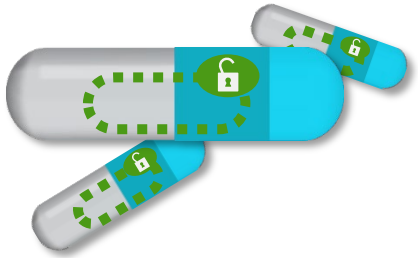
Trypsin activation (TAAP) releases free and active drug product

SUB-THRESHOLD

trypsin inhibitor



DOSE THRESHOLD

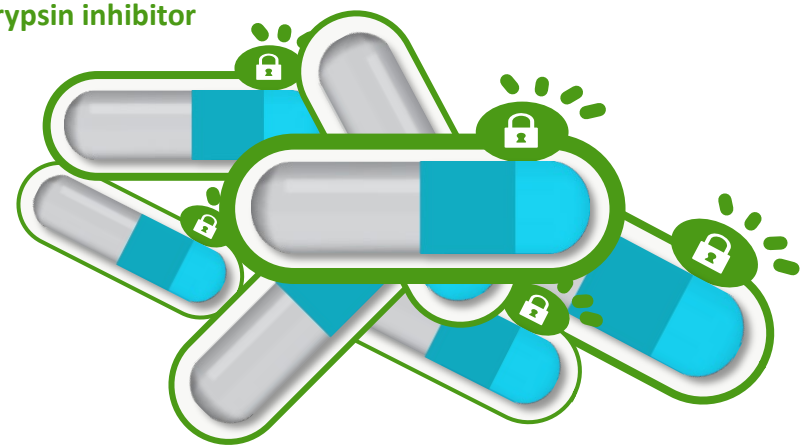


ACCIDENTAL OVERDOSE

A higher amount of MPAR (more nafamostat) begins to inhibit trypsin activity, limiting opioid release

ABOVE THRESHOLD

trypsin inhibitor



EXCESS MPAR DOSE

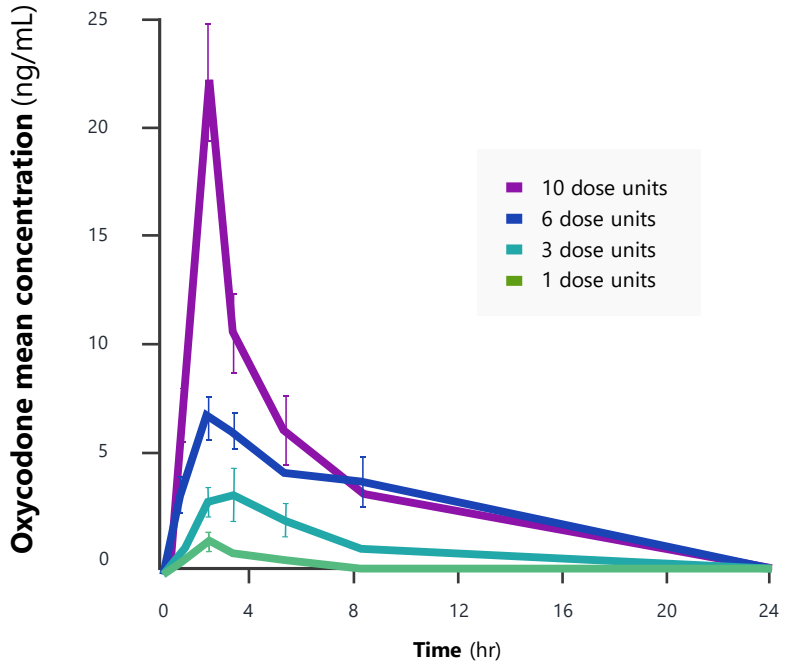
Trypsin Activation blocked / overdose averted

MPAR™ is only triggered by an overdose

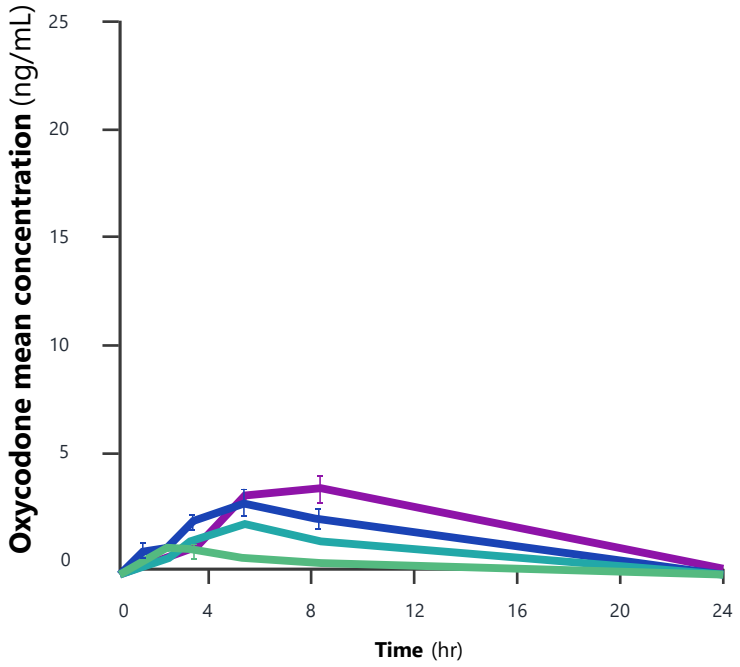
PF614-MPAR™ PRECLINICAL RAT DATA

Blocks trypsin activation and Oxycodone Release only if Overdosed

Without MPAR™
PF614 without nafamostat



With MPAR™
PF614 with nafamostat



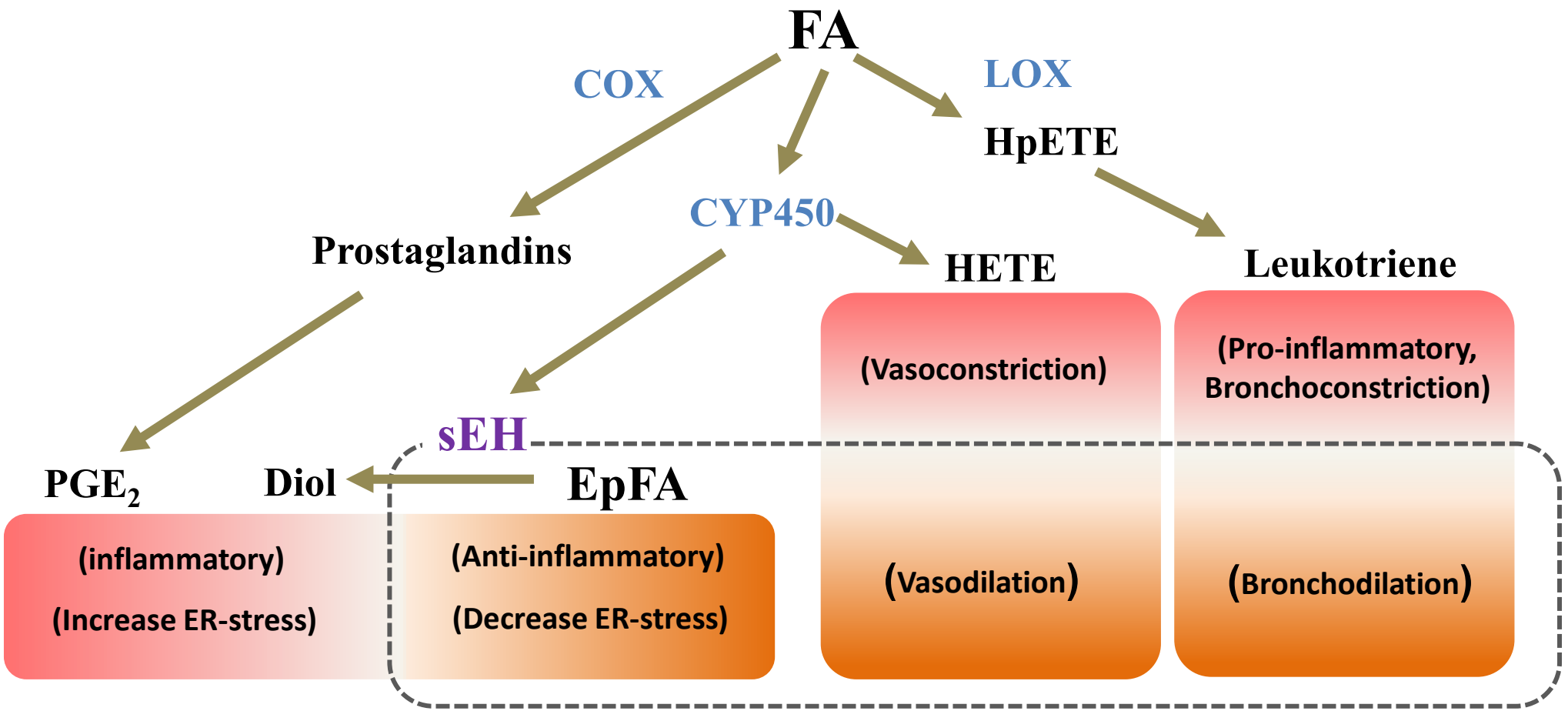
in rats n=4 / dose

Multi-Pill Abuse Resistance

- Combination product: PF614 and nafamostat
- Taken at prescribed doses there is no change in oxycodone release from PF614
- More than prescribed dose nafamostat blocks trypsin activation of PF614 reducing oxycodone release – averting OD
- **First human data announced May 2022**

EicOsis is developing a more efficacious and safer treatment for chronic painful conditions

EpFA balance the action of inflammatory lipids



McReynolds et al. 2020
Epoxy fatty acids are promising target for the treatment of pain, cardiovascular disease and other indications characterized by mitochondrial dysfunction, endoplasmic stress and inflammation

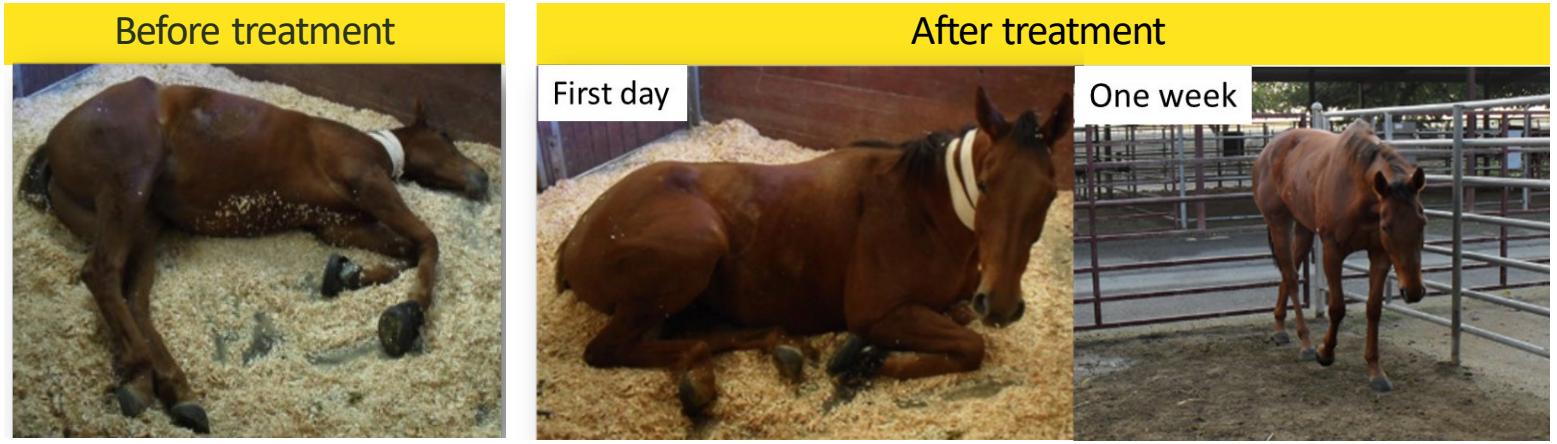
- EpFAs balance action of other oxylipins.
- Metabolism to diols abolished the beneficial actions of EpFAs.

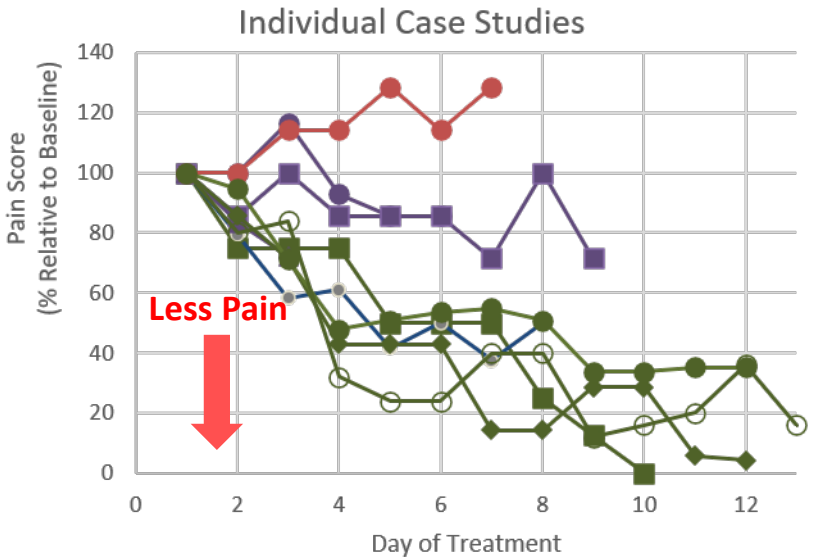
sEHI Treat Natural Disease in Animals

sEHI have strong efficacy in rodent pain models, but the translation of rodent models to humans is often questioned. sEHI also treat natural disease in animals, supporting translation to humans.

In equine laminitis, severe inflammation of the foot in horses, administration of an sEHI reduced pain and mortality ***when all traditional analgesics failed*** (Guedes *et al.* 2017).

Case #1





Guedes et al. Vet Anesth Analg. 2013 Jul;40(4):440-448
Guedes et al. Equine Vet J. 2017 May;49(3):345-351

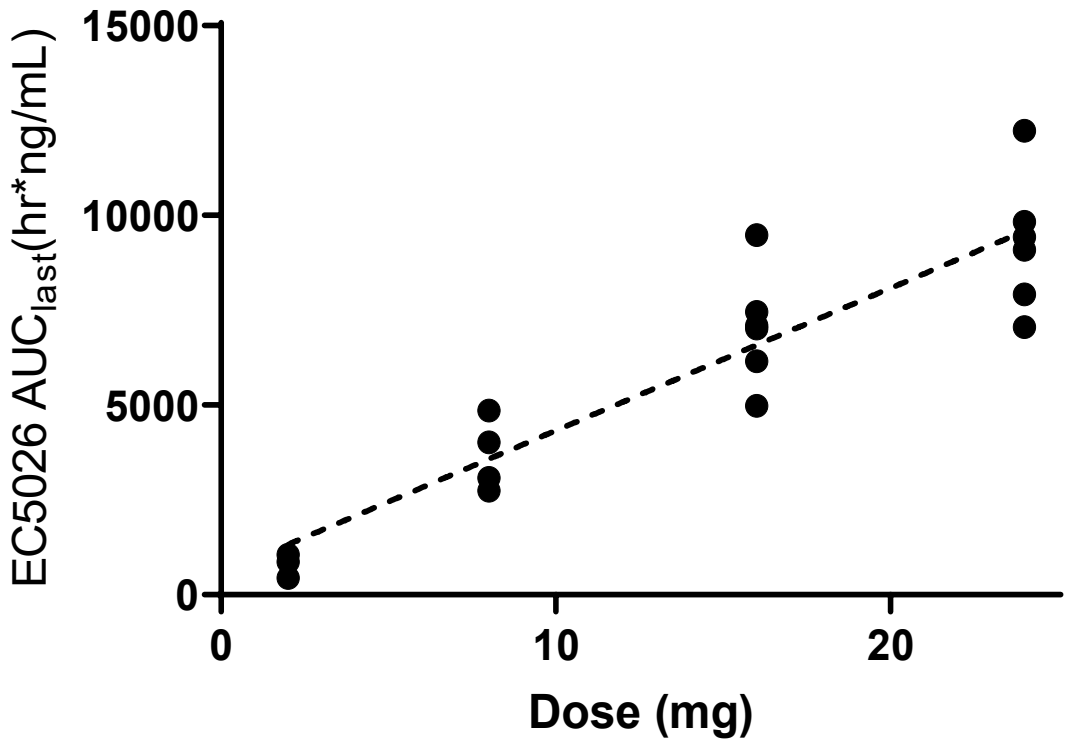
EC5026 Demonstrated Phase 1a Clinical Safety in Healthy Volunteers

EC5026 Phase 1a Clinical Results

In a Phase 1a single ascending dose (SAD) clinical study, oral EC5026 was administered in in healthy volunteers and monitored in plasma over 14 days:

- No drug-related adverse events were observed
- AUC was linear with EC5026 dose
- $T_{1/2}$ of about 2 days, supporting once daily oral dosing

Phase 1a Fed-fasted clinical study completed



EC5026 exposure (AUC) is linear with dose

Hammock et al. J Med Chem. 2021 Feb 25;64(4):1856-1872

Typical Clinical Development Plan: Chronic Pain Indication

Phase 1a: Single Ascending Dose (SAD) Healthy Volunteers

- **Goal = Safety + PK/ADME**
- **6 Cohorts, M/F, 6 Active + 2 Placebo per cohort**
- **Sentinel Dosing; Safety Review Team**
- **48 Total Subjects**
- **Time = 3-6 months (active phase) + analysis = 6-9 months**

Phase 1b: Multiple Ascending Dose (MAD) Healthy Volunteers

Phase 2a: Dose-ranging Efficacy Study in Target Patient Population

Phase 2b: Confirmatory Effic

Phase 3: Pivotal Efficacy St
Open-Label Safety

Time to Determine Proof of Concept (POC) Efficacy = 2.5 to 3+ years

Cost = $20+ million before you know "if the drug works"

FDA GUIDANCE:
Some classes of drugs (e.g., many cytotoxic or biological agents) are commonly introduced into initial clinical trials in patient volunteers rather than healthy volunteers. Typically, patients are used instead of healthy volunteers when a drug is suspected or known to be unavoidably toxic.

Dual Phase 1 Concept: Healthy Subjects & Chronic Pain Subjects

Use traditional Single Ascending Dose (SAD) PK & Safety Assessments in two consecutive, interleaved populations. Pain Assessments in Chronic Pain Group.

Week	Healthy Volunteers	Chronic Pain Subjects
1	Cohort 1a (N=2 Sentinel)	
2	Cohort 1b (N=6 Sentinel)	
3		Cohort 1c (N=2 Sentinel)
4		Cohort 1d (N=6 Sentinel)
5	Cohort 2a (N=2 Sentinel)	
6	Cohort 2b (N=6 Sentinel)	
7		Cohort 2c (N=2 Sentinel)
8		Cohort 2c (N=6 Sentinel)
9	Cohort 3a (N=2 Sentinel)	
10	Cohort 3b (N=6 Sentinel)	
11		Cohort 3c (N=2 Sentinel)
12		Cohort 3d (N=6 Sentinel)
13	Cohort 4a (N=2 Sentinel)	
14	Cohort 4b (N=6 Sentinel)	
15		Cohort 4c (N=2 Sentinel)
16		Cohort 4d (N=6 Sentinel)

Expected Efficacy Dose Levels

Dual Phase 1 Concept

- Assures maximum safety for both populations (Healthy Volunteers and Chronic Pain Subjects)
- Chronic Pain Subjects remain on current meds (no destabilization) and are trained to report pain accurately (reduced variance)
- Requires evaluation of drug(s) expected to have onset of therapeutic response within 12-24 hr
- Assures limited resources are directed only toward drugs that achieve initial Target Product Profile for efficacy and safety
- Reduces exposure to ineffective drugs
- Accelerates development of effective analgesics to address Opioid Crisis

Caveat: *"This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease"*

NIH Blueprint

Neurotherapeutics Network

January 2016:
EicOsis receives a $4 million federal grant to target diabetic nerve pain (NINDS)

EC5026 chosen as clinical candidate

2018-2022:
Additional $6 million funding from NIDA +
$5 million funding from Open Philanthropy to Initiate Proof of Concept clinical studies

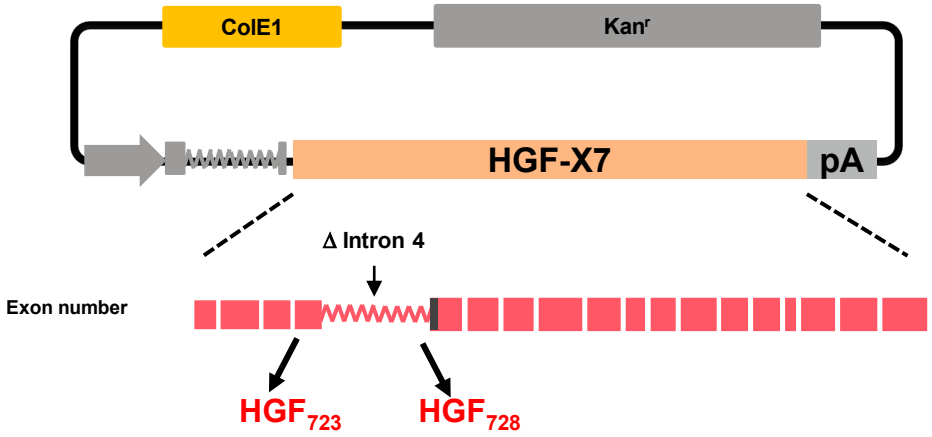
HELIXMITH

Novel Concept:
Regenerative Medicine for Neuropathy, Neuromuscular, and Neuroischemic Diseases Using a Gene Therapy Approach

Helixmith Co., Ltd, Seoul, South Korea
Helixmith USA Inc., San Diego, CA

Lead Asset : Engensis

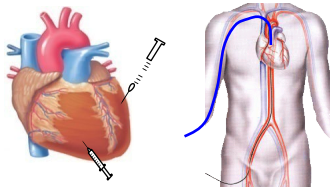
Engensis: Plasmid DNA engineered to simultaneously express two isoforms of **HGF (Hepatocyte Growth Factor)**

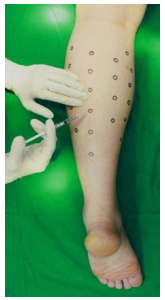


Freeze-dried

Injection method: Intramuscular (I.M.) injection at the target site, tailored to the disease of interest

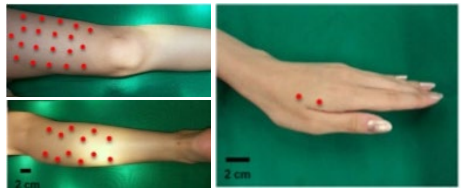
Heart





Calf muscle

Upper and Lower Limbs



Product characteristics

- **Therapeutic Gene:** HGF (Hepatocyte Growth Factor)
- **Two isoforms encoded:** HGF_{723} + HGF_{728}, mimicking the human body
- **High level gene expression:**
  - Promoter
  - UTR
  - Intron
- **Formulation:** Freeze-dried, for convenient supply chain (only DNA to do so in industry)

Potential Benefits of I.M. Injections of Engensis

1. Regeneration of the CNS and PNS neurons, motor and sensory neurons, and Schwann cells

2. Anti-neuroinflammatory activities by controlling the expression of inflammatory cytokines

3. Control of activated microglial cells in the spinal cord

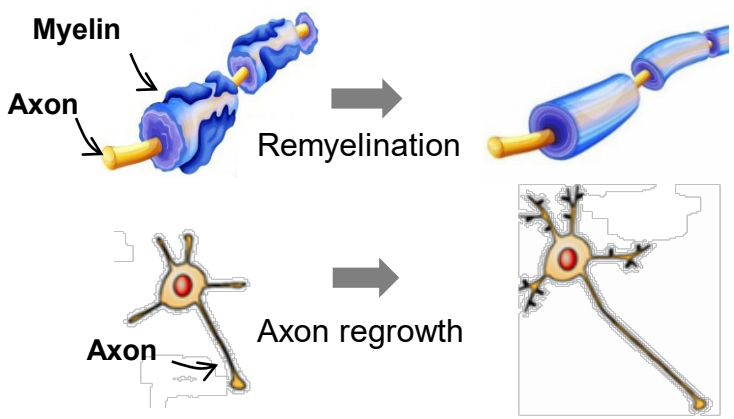
4. Improvement in the microvasculature environment

5. Long-term analgesic effects

6. Improvement in muscle atrophy

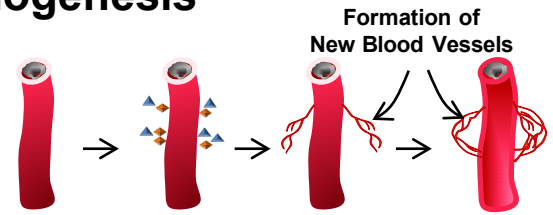
Mode of Action

1. Regeneration of damaged nerves



2. Analgesic effects by controlling the expression of pain factors (CSF-1, IL-6, α2δ1, 5-HTT, etc.)

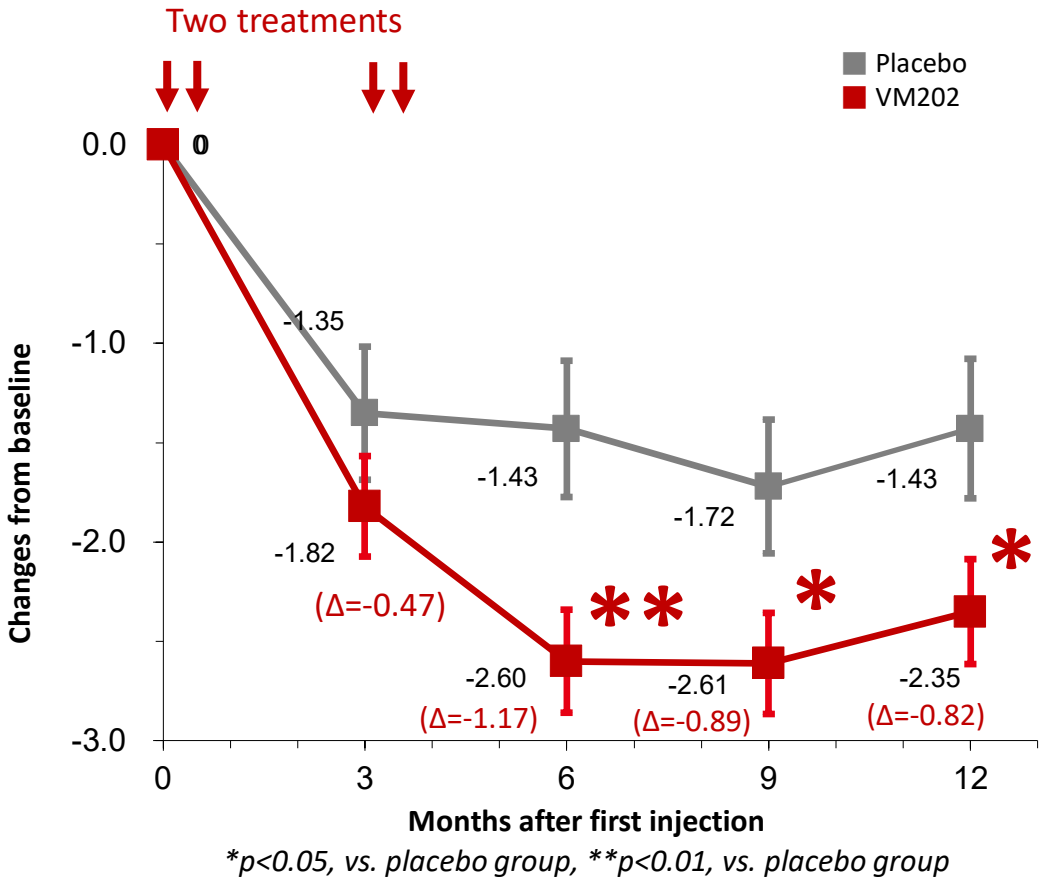
3. Angiogenesis



4. Control of miR206, HDAC4, atrogin-1 and MuRF1
→ Amelioration of muscle atrophy

Phase 3-1B Study: Effect on Pain Severity

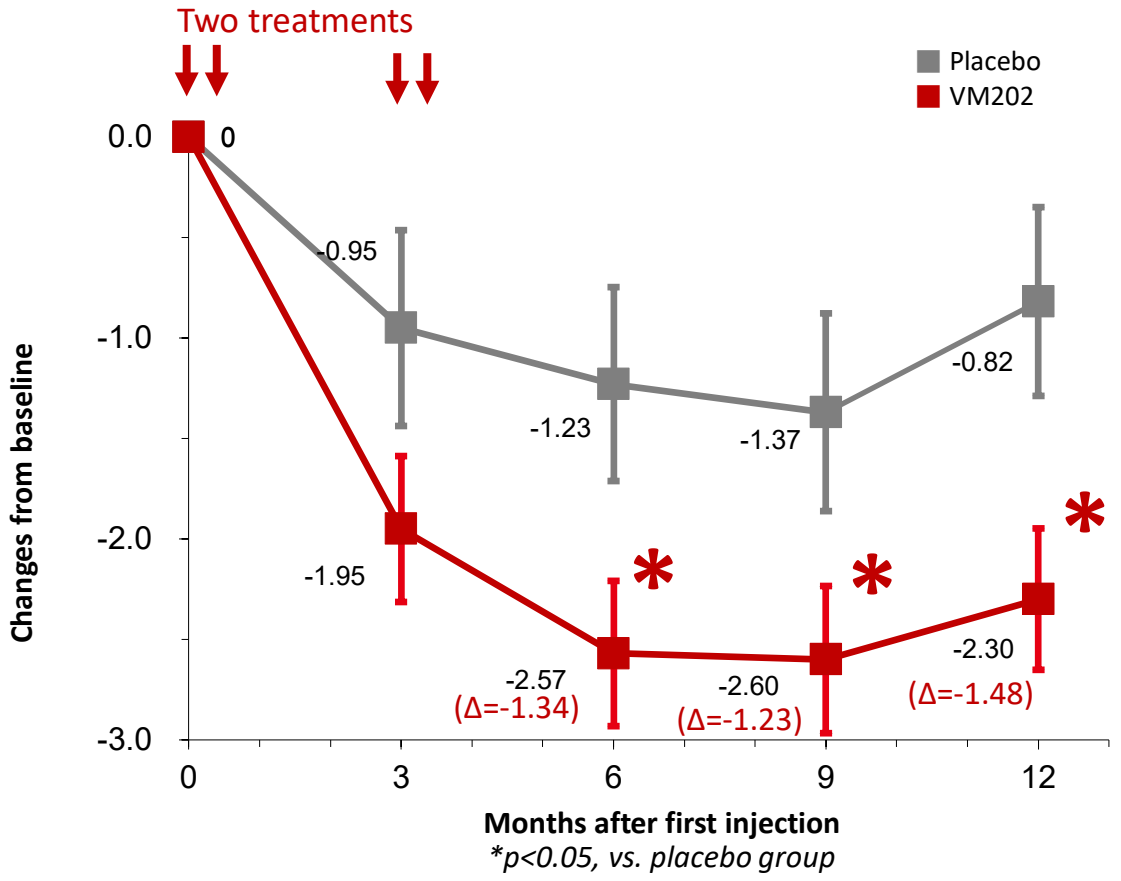
Total population (N=101)



*p<0.05, vs. placebo group, **p<0.01, vs. placebo group

Long-term, high level pain-relieving effect in all subjects

Subjects NOT on pregabalin and/or gabapentin (N=53)



*p<0.05, vs. placebo group

Much higher analgesic effect in subjects not on gabapentinoids

Kessler et al., Clin Transl Sci 2021

VMDN-003b: Conclusion & Significance

Data from the VMDN-003b Study were Highly Similar to those from Phase 2

① **Safety:**
Little difference between placebo and Engensis (VM202) groups

② **Potential for long-term analgesic effect:**
The Δ values between Engensis (VM202) and placebo were 1.1, 0.9, 0.9 at 6, 9, 12 months, respectively (p=<0.05) in the ITT (N=101) population

③ **Higher pain reducing effects in patients NOT taking gabapentin and/or pregabalin (N=53):**
The Δ values were even greater: 1.3, 1.2, 1.5 at 6, 9, 12 months, respectively (p=<0.05)

④ **Regenerative Medicine Potential:**
Analgesic effect was observed, even in the absence of Engensis (VM202) DNA and HGF protein expression, for 8 months after the last injection of Engensis (VM202).

RMAT Designation
(Regenerative Medicine Advanced Therapy)

Engensis (VM202) for Painful DPN was granted RMAT by FDA on 21 May 2018,
The First and Only RMAT Designation for Pain

Eligibility	• Drug that are regenerative medicine therapies • **Drugs intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition** • Preliminary clinical evidence indicates potential to address unmet medical needs
Benefits	• Includes all of the benefits of **Fast Track** and **Breakthrough** designation programs • Allows **shorter timeline for BLA approval** including frequent interactions with FDA
RMAT Status	• Total 52 RMAT Designation granted[1] • Among RMAT designations for gene therapies, **only two were granted for the treatment of prevalent diseases**: ✓ Engensis (VM202): Diabetic Peripheral Neuropathy ✓ VY-AADC: Parkinson's Disease

[1]Cumulative CBER Regenerative Medicine Advanced Therapy (RMAT) Designation Requests Received by Fiscal Year, FDA website, Data as of September 2020

Conclusion

- Three different clinical-stage analgesic compounds are presented that are radically different from existing analgesic drugs
- Each meets the criteria of addressing the urgent need for new pain drugs with either less or no addiction potential compared to higher efficacy analgesics (e.g. opioids) currently available for acute or chronic pain
- Major hurdles remain to bring each of these drugs to NDA / BLA approval
- Advancement of any one of these drugs could represent a major change in the way that we practice pain medicine

Divinium est opus sedare dolorem

(Divine is the work to subdue pain)

Hippocrates (? 460 - ? 377 B.C.)

If it were easy to build new drugs, safely …
anyone could do it.

Anon (2014)