DESIGNING A BETTER ANALGESIC

Lumekefamide: A Dual-Mechanism Novel Peptide Analgesic for Surgical and Trauma Pain Care

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Mechanism • PK Compartmentalization • Naloxone Reversibility • HAL Trial Design

Military Health System Symposium (MHSRS)
Breakout Session: Preserving Warfighter Performance & Readiness Through Improved Battlefield Pain Control
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The Central Tension in Pain Medicine

✓ WE NEED

- Potent, fast-onset analgesia
- Sustained efficacy (no dose-escalation)
- Suitable for acute AND chronic pain
- Broad prescriber access
- No REMS, no DEA scheduling hassle
- Safe in vulnerable populations
- No Respiratory Depression

VS

✗ CONVENTIONAL OPIOIDS BRING

- Respiratory depression (μ2-mediated)
- Addiction & physical dependence
- Rapid tolerance (dose escalation)
- Schedule II prescribing friction
- REMS compliance burden
- 80,000+ overdose deaths/year in US

CDC WONDER Database, 2022; SAMHSA National Survey on Drug Use and Health, 2022. Opioid overdose death data reflects 2022 US figures.

The Reason We Are Here Today

Battlefield Pain Management

We are developing a range of fast-acting pain relief treatments for use on the battlefield during field care and evacuation. DSUVIA is a currently available, safe solution that can be used without an IV. Rapid-acting non-opioid medications, such as ketamine, are also under development. The focus is on pain solutions that will be safe with repeated use during prolonged field care and evacuation.

Operational Medical Systems

Program Management Office

We are the DOD's leading force in medical development and acquisition, focused on enhancing warfighter lethality and readiness. We develop and deliver next-generation, world-class medical capabilities that empower combatant commanders in Large-Scale Combat Operations, particularly within austere environments. Our mission is twofold: to save lives on the battlefield and to swiftly return injured service members to duty.

DHA
Defense Health Agency ®

https://dha.mil/Offices-and-Programs/OPMED

A Century of Discovery: From Frog to Pharmacology

Boulenger names the species in 1882. Erspamer finds the molecule in 1981. 45 years later — a DEA-confirmed non-scheduled analgesic.

Phyllomedusa sauvagei

Waxy monkey tree frog — Amazon Basin

1882

George Albert Boulenger classifies Phyllomedusa sauvagei in his Catalogue of the Batrachia Salientia — the frog's opioid secret would remain hidden for nearly 100 years
"Guardian of the Leaf" — Phyllo (leaf) + medousa (guardian)

1981

Vittorio Erspamer's team isolates dermorphin from P. sauvagei skin — 30–40× more potent than morphine, with an unprecedented D-amino acid structure never before seen in a vertebrate

1985

RCT: 20 mcg intrathecal dermorphin > 500 mcg morphine — 43h vs 34h analgesia

2010+

PVP Labs develops lumekefamide (DMTP/Taphalgin®)
6 clinical trials, 100,000+ human exposures

2026

DEA confirms: lumekefamide is NOT a controlled substance under CSA

1. Boulenger GA. Catalogue of the Batrachia Salientias. Ecaudata. London: British Museum; 1882 (P. sauvagei first classification). 2. Montecucchi PC, et al. Int J Pept Protein Res. 1981;17(3):275-83 (dermorphin isolation). 3. Erspamer V, et al. Proc Natl Acad Sci. 1989;86:5188-5192. 4. Basso N, et al. Peptides. 1985;6(Suppl 3):177-179. PMID: 3831962 (intrathecal dermorphin RCT; n=150 elective surgical patients). 5. PVP Labs, Data on File. IQVIA Human Exposure Database, 2025. 6. DEA Diversion Control Division Determination Letter, March 2026.

Meet the Source: Phyllomedusa sauvagei

The Waxy Monkey Tree Frog — classified 1882, pharmacologically famous 1981

Scientific name: Phyllomedusa sauvagei
Common name: Waxy Monkey Tree Frog
Habitat: Gran Chaco region — Argentina, Bolivia, Paraguay, Brazil
Classified: G.A. Boulenger, 1882 — named for Dr. Henri Émile Sauvage
Genus meaning: "Guardian of the Leaf" (phyllo + medousa)

"Somewhere in the Amazon rainforest, a waxy monkey frog sits motionless on a branch. It looks unremarkable. Green skin, sticky toes, big eyes. But this frog harbors something extraordinary in its skin secretions — a seven-amino-acid chain that changed our understanding of natural peptides forever."

The frog uses a waxy lipid secretion to protect itself from evaporative water loss in the semi-arid Gran Chaco. But its skin glands also produce over 200 bioactive peptides — a chemical arsenal refined over millions of years of evolution. Dermorphin is the most pharmacologically remarkable of them all. When a predator bites this frog, a cocktail of peptides floods the attacker — caeruleins, bradykinins, tachykinins, and opioid peptides that cause disorientation and sedation. Evolution spent millions of years perfecting what pharmaceutical chemistry has struggled for decades to replicate.

Lumekefamide is the synthetic distillation of that evolutionary masterpiece: four amino acids, engineered from dermorphin's scaffold, delivering potent analgesia without the opioid crisis's defining harms.

Boulenger GA. Catalogue of the Batrachia Salientia s. Ecaudata. London: British Museum; 1882. | Erspamer V, et al. Proc Natl Acad Sci. 1989;86:5188-5192. | SeekPeptides (2026). Dermorphin peptide benefits. seekpeptides.com.

The Molecule: H-Tyr–D-Arg–Phe–Gly–NH_2

Four residues. Two mechanisms. Zero scheduling.

Position 1	Position 2	Position 3	Position 4
Tyr	**D-Arg**	**Phe**	**Gly–NH_2**
Opioid pharmacophore μ-receptor binding anchor	The key innovation: D-amino acid → enzymatic resistance + mu-preferring binding profile	Aromatic recognition Receptor binding lock	Backbone flexibility C-terminal amide: stability + potency

DUAL MECHANISM: Mu-preferring opioid receptor agonist + Calcium channel modulation = **Analgesia with a potentially improved liability profile vs. conventional opioids**

1. Chaki K, et al. Peptides. 1990;11:139-144. 2. Schiller PW. AAPS J. 2005;7(3):E560-E565. 3. Mizoguchi H, et al. Peptides. 2011;32(2):421-427. 4. PVP Labs, Data on File. Calcium channel modulation characterization studies.

Mechanistic Differentiation: A Hypothesis Grounded in Receptor Pharmacology

μ1 RECEPTOR (LUMEKEFAMIDE TARGET)

- Supraspinal analgesia
- Peripheral antinociception
- Anti-allodynia (neuropathic pain)
- Sedation (mild, dose-dependent)
- Hypothermia (low doses)

DESIRED

D-Arg² drives μ1 selectivity

μ2 RECEPTOR (AVOIDED BY DESIGN)

- Respiratory depression
- Physical dependence & addiction
- Euphoria / reward pathway
- Constipation (GI dysmotility)
- Spinal analgesia (some)

AVOIDED

1. Pasternak GW. Clin Neuropharmacol. 1993;16(1):1-18 (mu receptor subtype pharmacology). 2. Wolozin BL, Pasternak GW. Proc Natl Acad Sci. 1981;78(10):6181-6185 (mu1/mu2 distinction). 3. Chaki K, et al. Pharmacol Biochem Behav. 1988;31(2):439-444 (D-Arg2 mu1 selectivity).

Distribution-Driven Pharmacology: PK Compartmentalization

CENTRAL NERVOUS SYSTEM

Peripheral Opioid Receptors
Primary compartment for lumekefamide
→ Rich analgesic effect
→ No CNS saturation

Blood-Brain Barrier → Limited but real CNS penetration
- Net +2 charge (D-Arg^2) limits passive diffusion
- Partial active transport observed — slower onset

Ca^{2+} Channel Modulation — The Second Mechanism
Operates at both peripheral AND spinal pain transmission sites
→ Non-opioid analgesic contribution → fills gap left by limited CNS opioid penetration

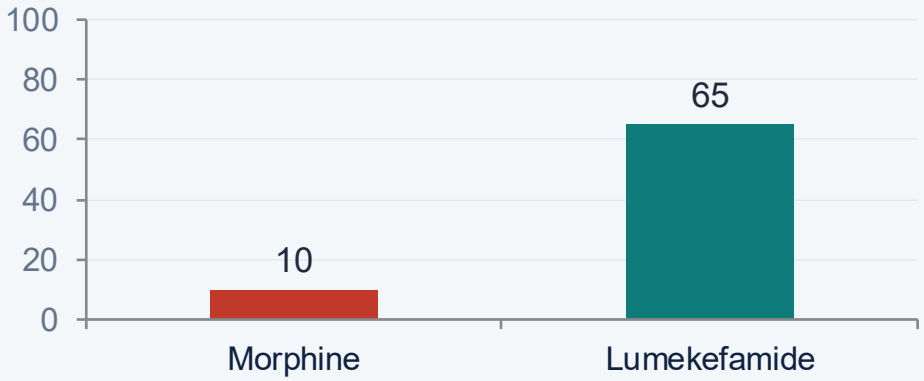
Clinical implication:
Potent analgesia WITHOUT the CNS saturation that drives addiction & respiratory depression

1. Szeto HH, et al. J Pharmacol Exp Ther. 2001;298:57-61 (PK of mu-selective tetrapeptides). 2. Ballet S, et al. J Med Chem. 2008;51(8):2571-2574 (BBB penetration, lipophilicity). 3. Zhao K, et al. J Pharmacol Exp Ther. 2003;304:425-432 (transcellular transport of cationic opioid peptides). 4. PVP Labs, Data on File. Calcium channel modulation studies.

Pre-Clinical Evidence: Tolerance & Safety Profile

Rodent models • Continuous IV infusion protocols • Structural analog data (dermorphin tetrapeptide class)

Tolerance Development (Continuous Infusion, Day 4)



17× Safer Respiratory Window

[Lys7]-dermorphin analog data: ratio of analgesic to respiratory-depressant dose is 17-fold more favorable than morphine.

1. Mizoguchi H, et al. Peptides. 2011;32(2):421-427 (bar chart: tolerance retention Day 4, rodent continuous IV infusion). 2. Chaki K, et al. Pharmacol Biochem Behav. 1988;31(2):439-444 ([D-Arg2]-dermorphin tetrapeptide analgesic potency). 3. De Castiglione R, Faoro F. In: Opioid Peptides. 1983 (17x resp window, [Lys7]-dermorphin analog data). 4. Negri L, et al. Br J Pharmacol. 1981;73(3):625-631 (tolerance and dependence profile vs morphine).

Human Clinical Evidence

6 completed clinical studies • 100,000+ documented human exposures (IQVIA) • Ex-US approvals (postoperative & cancer pain)

43.4h
Post-op pain relief
(vs 34.5h morphine)

25×
Lower dose than
morphine for superiority

78%
Patients needed
zero rescue analgesia

Zero respiratory depression events
reported in the 1985 pivotal intrathecal RCT (n=50 dermorphin arm)

1. Basso N, et al. Peptides. 1985;6(Suppl 3):177-179. PMID: 3831962 (intrathecal dermorphin in postoperative analgesia; n=150 elective surgical patients, chest/abdominal/pelvic procedures). 2. Keppel Hesselink JM, Schatman ME. J Pain Res. 2018;11:2991-2997 (rediscovery of dermorphin, RCT results). 3. PVP Labs, Data on File. IQVIA Real-World Exposure Database; 6 clinical studies (Phase I/II/III), ex-US.

Naloxone Reversibility: Safety Architecture Confirmed

The opioid emergency antidote works. Full stop.

Why Naloxone Reversibility Is Non-Negotiable for FDA — Any compound with opioid agonist activity must demonstrate complete reversal by naloxone to confirm mechanism-specific action. Irreversibility would signal additional, potentially dangerous mechanisms.

Full analgesic reversal

All antinociceptive effects of lumekefamide are completely blocked and reversed by naloxone, confirming pure opioid receptor-mediated analgesia

Ca^{2+} component separately characterized

The calcium channel modulation component can be distinguished mechanistically — this dual-mechanism clarity is a regulatory asset, not a liability

Consistent across routes & doses

Reversal confirmed whether lumekefamide administered IV, subcutaneously, or intrathecally, across the full analgesic dose range

1. PVP Labs, Data on File. Naloxone reversal studies across IV, subcutaneous, and intrathecal routes. 2. Basso N, et al. Peptides. 1985;6(Suppl 3):177-179. PMID: 3831962 (no respiratory depression in dermorphin arm; naloxone used in open-label preliminary studies to reverse nausea/vomiting, confirming opioid receptor-mediated effects). 3. FDA Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017.

The Regulatory Inflection Point: March 2026

"The DEA conducted a scientific review of the chemical structure of lumekefamide in accordance with the definitions within the CSA and its implementing regulations. Based on this review, DEA determined that lumekefamide is NOT a controlled substance or a listed chemical under the CSA."

— Drug Enforcement Administration, March 2026

Any MD can prescribe

No DEA controlled substance registration required. No Schedule II prescribing friction.

No supply limits

No 30-day caps, no refill restrictions from scheduling. Standard Rx workflow.

No production quotas

DEA aggregate production quotas don't apply. Scale to market demand.

No REMS likely

Opioid Analgesic REMS legal basis substantially weakened without scheduling.

1. DEA Diversion Control Division. Scheduling Determination Letter re: Lumekefamide. March 2026. 2. 21 U.S.C. §§ 811, 812 — Controlled Substances Act scheduling criteria. 3. FDA REMS Guidance. Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). Updated 2023.

Human Abuse Liability Trial Design: Implications

When your pharmacology predicts low abuse liability — your HAL design should confirm, not just describe

Why Lumekefamide Predicts LOW Abuse Liability

- Limited CNS penetration → reduced euphoria
- μ1 selectivity → avoids reward-pathway μ2
- Non-addictive profile in 100K+ exposures (IQVIA)

FDA Expects for Any Opioid-Mechanism NDA

- Randomized crossover vs. hydromorphone + placebo
- VAS Drug Liking as primary endpoint
- Maximum Drug Effect (Emax) + AUC comparisons

1

Population

Recreational opioid users (non-dependent) per FDA guidance
Screened for opioid familiarity

2

Comparators

Lumekefamide (3 doses)
Opioid (positive control)
Placebo — double-blind crossover

3

Key Endpoints

Drug Liking VAS (primary)
High VAS, Take Again VAS
PEG / ARCI scales

4

Strategic Insight

BBB-limited CNS exposure = lower Emax
Non-scheduled status pre-validated
DEA letter provides regulatory context

1. FDA Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017 (HAL study design). 2. Griffiths RR, et al. Drug Alcohol Depend. 2003;70(3):S77-S88 (Drug Liking VAS methodology). 3. PVP Labs, Data on File. IQVIA non-addictive safety profile; 100,000+ human exposures.

U.S. Development Strategy: Reshaping Acute Pain Development

Pre-IND / IND *Complete*	Phase 1 (US) *Near-term*	Phase 2 (US) *2027-28*	Phase 3 (US) *2029+*
• FDA pre-IND engagement done • Route: subcutaneous • Indication: acute post-op pain • 6 trials + 100K exposures cited	• Safety/PK in healthy volunteers • De-risked by international data • HAL trial concurrent • PK/PD compartment modeling	• Post-surgical pain (primary) • Military trauma (parallel) • Dose-finding vs active comparator • ePRO endpoints	• Pivotal RCT — FDA standard • Active + placebo controlled • NDA submission target • Non-scheduled labeling

Strategic Beachheads: Military medicine (battlefield analgesia, non-scheduled = simplified logistics) • Post-surgical hospital acute pain • Veterans health (VA formulary) • Veterinary medicine (equine/large animal)

PVP Labs, Data on File. Pre-IND FDA Meeting Summary. 2024. 100,000+ human exposures: IQVIA Real-World Database. 2024. Taphalgin® ex-US approvals: Russian Ministry of Health Registration; Singapore HSA Registration.

Implications for Pain Drug Development Strategy

Lessons for developers, regulators, and clinical trialists in this room

01

Pharmacology drives regulatory classification

A peptide's structural character — net charge, D-amino acids, molecular size — directly determines DEA scheduling fate. Structural design IS regulatory strategy.

02

PK compartmentalization is a safety feature

Designing for limited CNS penetration isn't a liability — it's the mechanism by which you avoid addiction and respiratory depression.

03

HAL design should follow pharmacology

When μ1 selectivity and limited CNS exposure are built in structurally, the HAL trial becomes confirmatory. Science frames the clinical program.

04

Ex-US data is underutilized in INDs

100,000+ human exposures is a key dataset. Used correctly, it compresses US development timelines materially.

05

Potential Non-scheduling is a commercial asset

Scheduling is the #1 prescriber barrier. Non-scheduled opioid-mechanism analgesics address the opioid crisis without sacrificing efficacy.

06

Nature's pharmacophores deserve rediscovery

The best analgesic scaffold in evolution sat in a paper cited 15 times since 1985. Dermorphin's legacy: revisit natural product pharmacology.

1. Ballet S, et al. J Med Chem. 2008;51:2571-2574 (structural determinants of BBB penetration). 2. FDA HAL Guidance, 2017 (HAL design confirmatory framework). 3. Keppel Hesselink JM, Schatman ME. J Pain Res. 2018;11:2991-2997 (dermorphin rediscovery). 4. PVP Labs, Data on File. IQVIA 100,000+ exposure data.

CAN OPIOID EFFECTIVENESS BE PRESERVED WHILE MATERIALLY REDUCING CENTRAL RISK?

Yes.

Lumekefamide is the Emerging Story .

Joe Stauffer, DO, MBA, FAPCR | Chief Medical Officer, PVP Labs

Taphalgin® | Lumekefamide | [D-Arg²]Dermorphin-(1-4) amide | DMTP

IP protected to 2036 in 31 countries • Pre-IND FDA engagement complete • DEA non-scheduling confirmed March 2026

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Thank You

"We can give you enough medication to alleviate the pain, but not enough to make it fun."

The New Yorker and The Pharmaceutical Institute Present: Laughing at Pharma. 2004