



*Next Generation in
Pain Pharmaceuticals...*

PHOENIX[™]
P h a r m a L a b s

Executive Summary

- We are **Phoenix PharmaLabs**, a preclinical stage pharmaceutical company, driven by a **mission to bring to the healthcare community a potent, safe pain therapy WITHOUT the risk of abuse and addiction**
- The U.S. Council of Economics Advisors estimated that the opioid crisis cost the U.S. economy over \$500B in 2015, and rising – there is substantial unmet need for non-addictive pain therapeutics
- Our **lead candidate, PPL-103**, is a novel new class of opioid with robust preclinical validation of:
 - Analgesic efficacy (10x potency of morphine)
 - No death from overdose
 - Low risk of abuse/addiction
- We have raised ~\$6M to date through two seed rounds and grants from the U.S. Army and NIH/NIDA, plus substantial investments-in-kind
- **We are now seeking \$10-15M to support clinical development of PPL-103 through Phase 2a Proof-of-Concept**
- We are preparing to enter a Phase 1 SAD/MAD study in mid-2020, and estimate a 3 year development path to a Phase 2a readout (mid-year 2022)
- PPL-103 is on a path to capture a sizeable portion of **the \$30B opioid therapeutics market**, representing a **substantial commercial opportunity**, with few other competitive products in development

Opioids are the most widely prescribed drugs for moderate to severe pain but their use is plagued by abuse and addiction

Substantial Market Size and Prescription Volumes

Annual Opioid Sales



Key Takeaways

- 192 million opioid prescriptions written in U.S. in 2017
- Global market projected at ~\$35B by 2025
- **Many people in the world are in severe pain** without access to opioids because of the addiction liability

High Unmet Need for Addressing Abuse Liability and Side Effects

Euphoria Leading to Abuse and Addiction

- **ALL** opioid analgesics on the market cause euphoria, which often leads to addiction
 - Approximately 80% of opioid addictions start after taking prescription opioids (CDC)

Death from Overdose

- 47,000 opioid overdose deaths in 2017
- CDC states that *this is a major public health problem that is getting rapidly worse*

Additional Side Effects

- Constipation, respiratory depression and physical dependence / withdrawal are common among opioid patients

Phoenix PharmaLabs was founded with the mission to develop a novel potent opioid analgesic with minimal abuse liability

Core Value Proposition

- 1 We believe the healthcare community deserves **potent pain therapy without abuse and addiction or death from overdose**
- 2 **Substantial investment returns** will be generated by **addressing this substantial unmet need** and bringing to market a potent analgesic with minimized liability of abuse
- 3 **PPL-103**, the lead product of Phoenix PharmaLabs, is positioned to deliver this value
 - Moderate agonist/antagonist across all three main opioid receptors as opposed to stimulating the Mu receptor alone
 - **Strong IP: composition of matter, methods and use** in U.S. & various other geographies
 - Robust **validation in preclinical models**; potent analgesic & minimal risk of abuse

Management Team

John Lawson, Ph.D. *Founder, Board Chairman, Chief Scientist*

- Primary developer of PPL I.P.
- Former Head of Neurochemistry R&D at SRI International

Bill Crossman *President, CEO, Board Member*

- Has launched and developed numerous successful early stage technology companies
- Experience as CEO, CFO, CDO across a range of startups and Fortune 500 companies

Lawrence Toll, Ph.D. *Chief Neuropharmacologist, Board Member*








- Co-discover of the nociceptin opioid peptide
- Professor of Biomedical Sciences, Florida Atlantic University
- Former Director of Neuropharmacology Department at Torrey Pines Institute for Molecular Studies and SRI International
- Author of 130+ peer-reviewed publications

Timmy Chou *Vice President, CFO, Board Member*

- Founding Partner, Spectra Consulting Group
- Experience as CEO/CFO of numerous emerging companies

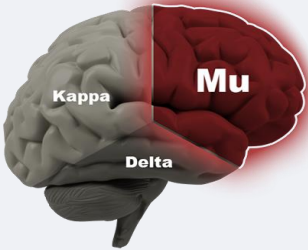
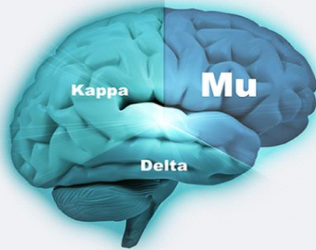
PPL-103 is a novel new class of opioid analgesic with low risk of abuse and limited side effects

PPL-103 Product Profile

 Robust Analgesic Potency	10x the potency of morphine
 Orally Active	As opposed to morphine which relies on IV administration
 No Euphoria or Abuse-Liability	No self-administration preference in correlative animal models
 No Dysphoria	No aversion - unlike kappa opioids
 No Physical Dependence	No withdrawal symptoms
 No Death from Overdose	Even at 350x dose
 No Constipation	Even at 100x dose

From Jain's Pain Therapeutics: "Phoenix [PharmaLabs Inc] is developing a new class of opioids with partial mu/delta/kappa-receptor activity allowing them to be moderately active at all three pain receptors. This balanced partial activity appears to allow full pain relief while eliminating or reducing such side effects as respiratory depression and addiction..."

PPL-103's unique profile has more balanced partial activity across all three main opioid receptors

Mu Opioids (ALL Current Opioids on the Market)	PPL-103
	
<ul style="list-style-type: none"> • Aggressively stimulate the mu receptor • Includes: morphine, oxycodone, hydrocodone, methadone, fentanyl, etc. – and heroin • Produce euphoria (abuse / addiction) • Death from overdose • Physical dependence / withdrawal • Constipation 	<ul style="list-style-type: none"> • PPL-103 is a partial agonist/antagonist across all three opioid receptors – mu, kappa & delta <ul style="list-style-type: none"> • Derives analgesic potency from all three receptors – without the side effects of either mu or kappa. • Functions as a potent analgesic WITHOUT euphoria / abuse & addiction • No death from overdose • No physical dependence / withdrawal • No constipation

Opioid Receptor Overview	Analgesic Efficacy:	Mu	Kappa	Delta
	Psychotropic Effect:	Potent	Potent	Mild
		Euphoria	Dysphoria	None

PPL-103 has strong binding affinity and is a partial agonist/antagonist across all three main opioid receptors

This drives increased potency and reduces the euphoria and abuse liability associated with mu opioids such as morphine and oxycodone

Opioid Receptor Binding Affinities

Compound	Mu Ki (nM)	Delta Ki (nM)	Kappa Ki (nM)
DAMGO	0.88 ± 0.07	300.0 ± 58.6	305.5 ± 46
DPDPE	503.6 ± 10.0	1.59 ± 0.08	>10,000
U69593	1,145 ± 335	>10,000	1.6 ± 0.26
morphine	1.1 ± 0.05	140.0 ± 1.5	46.9 ± 14.5
buprenorphine	1.5 ± 0.8	4.5 ± 0.4	0.8 ± 0.05
PPL-101	0.35 ± 0.04	3.97 ± 1.41	0.43 ± 0.11
PPL-103	0.36 ± 0.11	2.47 ± 0.105	0.29 ± 0.03

Functional Receptor Activity Assays

Compound	Mu		Delta		Kappa	
	EC ₅₀ (nM)	% Stimulation	EC ₅₀ (nM)	% Stimulation	EC ₅₀ (nM)	% Stimulation
DAMGO	13.7 ± 5.2	100	>10,000		>10,000	
DPDPE	>10,000		1.3 ± 0.5	100	>10,000	
U69593	>10,000		>10,000		78.4 ± 8.8	100
morphine	16.0 ± 1.0	97.6 ± 1.0	412 ± 12	78.1 ± 0.9	575 ± 81	24.9 ± 1.9
buprenorphine	2.3 ± 1.7	19 ± 05	flat		flat	
PPL-101	0.3 ± 0.09	12.2 ± 2.9	39.6 ± 6.30	22.4 ± 5.83	15.2 ± 2.5	62.6 ± 0.33
PPL-103	4.30 ± 2.1	22.6 ± 0.05	9.01 ± 2.64	39.8 ± 3.9	2.99 ± 0.92	41.7 ± 5.0






















Key Takeaways

- PPL-103 has strong binding affinity at all three opioid receptors
- *Note: The lower the Ki, the stronger the binding affinity*

Key Takeaways

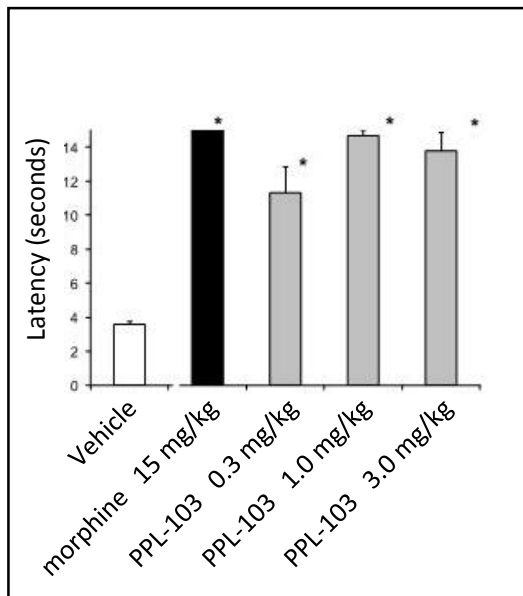
- PPL-103 is a moderate agonist/antagonist at all three main opioid receptors (with low agonism at the Mu receptor and moderate Delta/Kappa activity)
- *....as opposed to mu opioids, which disproportionately stimulate the mu receptor*

PPL-103 has been validated in preclinical models with strong correlation to human results

Characteristic	Mu Opioids	Kappa Opioids	PPL-103
Significant Euphoria (CPP/SA)	 Yes	 No	 No
Significant Dysphoria (CPA)	 No	 Yes	 No
Lethal Respiratory Depression at Moderate Dose	 Yes	 No	 No
Significant Constipation	 Yes	 No	 No
Withdrawal Symptoms	 Severe	 No	 No
Sustains Without Opiate Withdrawal	 Yes	 No	 Yes
Drowsiness	 No	 Strong	 Mild

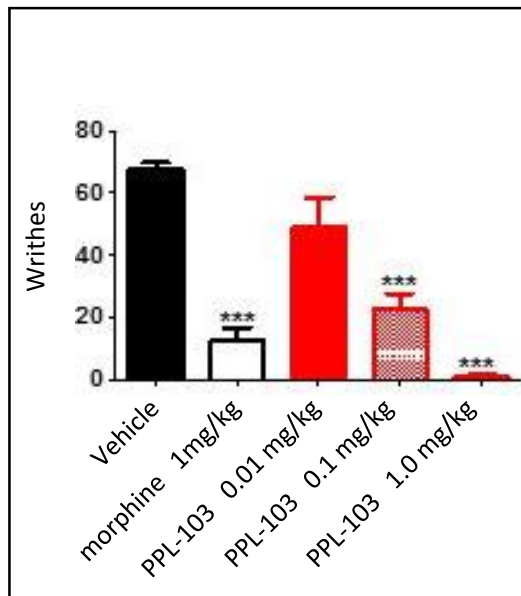
PPL-103 shows potent analgesic efficacy in multiple preclinical models for acute pain

Tail Flick Assay



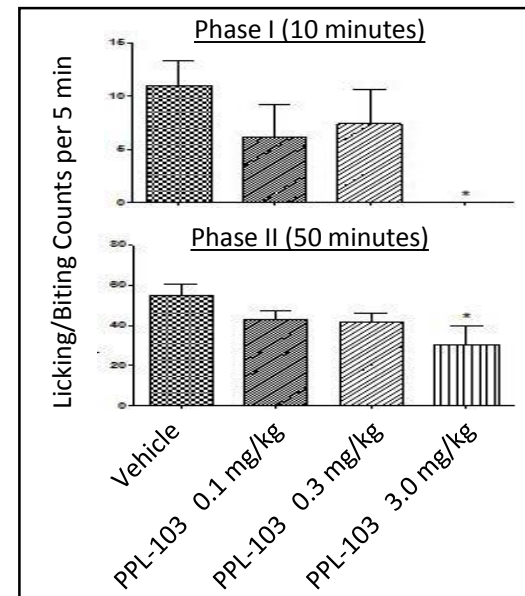
- The Tail Flick Assay is an acute pain-response test
- PPL-103 demonstrates analgesic efficacy at a low effective dose
- *10x potency of morphine*

Acetic Acid Assay



- The Acetic Acid Writching Model measures response to visceral pain
- PPL-103 acts as an effective analgesic, again with 10x the potency of morphine

Formalin Assay



- The Formalin Assay measures response to inflammatory pain
- In the Formalin Assay, orally administered PPL-103 is nearly as potent as IV-administered morphine
- PPL-103 is an effective oral analgesic for inflammatory pain

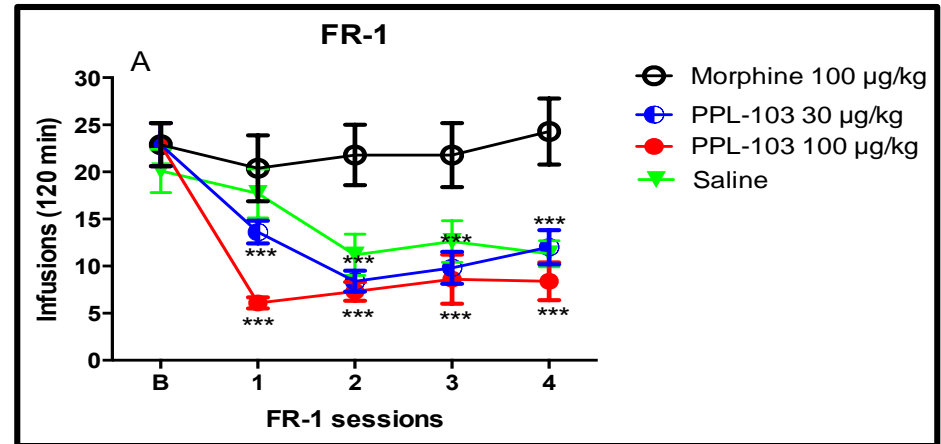
PPL-103 is not self-administered in the Rat Self-Administration Paradigm, which suggests very low likelihood of abuse in humans

What is the Self-Administration Paradigm in Rats?

- This assay is the FDA gold standard for determining whether or not a compound is likely to be addictive
- Research has shown that this study has a very high correlation to Human Abuse Liability (HAL)*

* "The predictive validity of the rat self-administration model for abuse liability"
O'Connor et al. *Neuroscience & Biobehavioral Rev.* 35:912-938, 2011

PPL-103: Rat Self-Administration Study

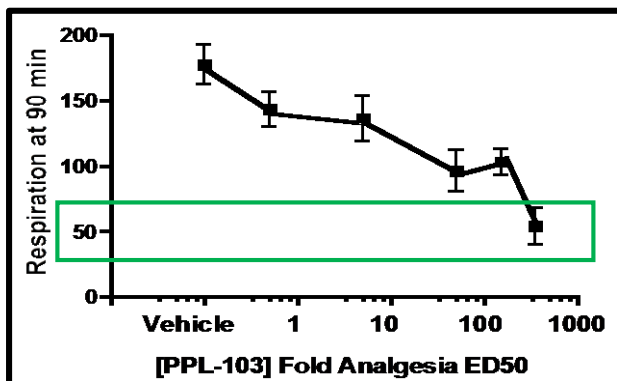


Key Takeaways

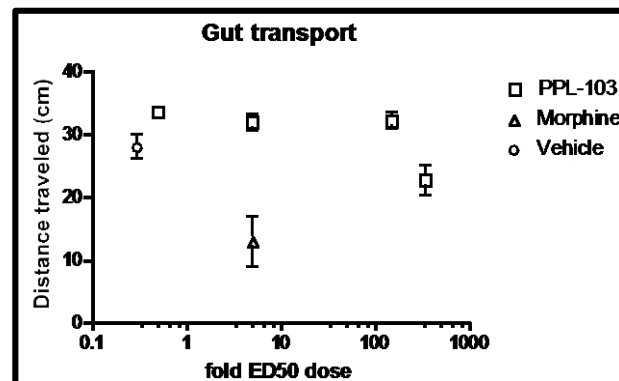
- This study suggests that PPL-103 will not be abused in people
- Level of PPL-103 self-administration is similar to saline, indicating no euphoria or dysphoria - compared to active self-administration of morphine
- Additional preclinical studies measuring euphoria (CPP/CPA, ICSS) have been conducted, yielding similar results

PPL-103 does not induce constipation and has minimal effect on respiratory depression in preclinical models

Respiratory Depression



Gut Transport (Constipation)



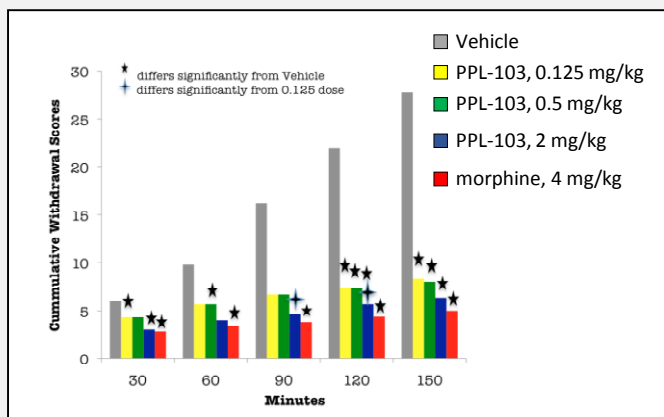
- **Even at 350x its ED50, PPL-103 is not lethal**
 - Respiratory Depression is the leading cause of opioid overdose death
- PPL-103 causes only a 25% decrease in respiratory depression up to 30 mg/kg (150x its tail-flick ED50)

- The Gut Transport test measures the rate that charcoal passes through the intestines
- PPL-103 does not induce any measurable constipation up to 50 mg/kg (250x its ED50 dose)
- By comparison, morphine causes a 50% decrease in gut transport at 10 mg/kg (only 5x its ED50 dose)

PPL-103 also shows promise for use in both opioid addiction therapy and cocaine addiction therapy

PPL-103 Shows Promise as Opioid Addiction Therapy

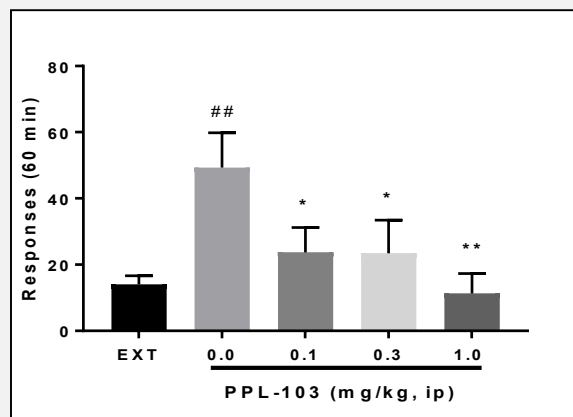
Effect of PPL-103 in Single Dose Suppression Assay in Rhesus Monkey



- PPL-103 blocks withdrawal in morphine-dependent monkeys
- It offers very promising use for addiction therapy as a preferred substitute for methadone, buprenorphine and Suboxone, since those drugs are, in and of themselves, addicting opiates that addicts typically have to remain on for life

PPL-103 Shows Promise as Cocaine Addiction Therapy

Effect of PPL-103 on Cocaine-Prime Induced Reinstatement of Cocaine Seeking



- PPL-103 blocks cocaine seeking behavior even when given at very low doses
- Further studies in progress in collaboration with NIH and NIDA
- There are currently no cocaine addiction therapies on the market

PPL-103 has relatively low clinical translation risk due to a strong predictive correlation between animal models and human results

Relative Translational Risk

- There is a great deal of longitudinal data supporting the relationship between the performance of mu, kappa and delta opioids in animal models compared to equivalent studies in humans.
- The predictive validity of the animal studies of PPL-103 is relatively high compared to most new chemical entities (NCEs) at the preclinical stage. The predictive correlation between studies of euphoria in animals and studies of abuse and addiction potential in humans is extremely high.

- Translational risk refers to the relative predictive correlation between animal and human results
- All preclinical NCEs have translational risk.
- Most NCEs have relatively little or no data supporting a positive predictive correlation between animal studies and human results.

We have received ~\$6M in funding to date from U.S. Army grants, NIDA grants, and two private seed rounds

Funding to Date

Grants from U.S. Army and NIDA

- Strong validation from U.S. Army and National Institute on Drug Abuse (NIDA)
 - \$2.7M grant awarded from the DOD / U.S. Army Medical Research Acquisition Activity (2018)
 - \$400K in direct NIDA grants, plus many additional studies sponsored by NIDA

Seed/Angel Rounds

- \$1.1M raised on NetCapital funding portal, oversubscribed through Regulation CF (March 2019)
- \$2.0M raised through early angel round
- Substantial investments-in-kind by management, scientists, consultants and various service providers



We are seeking \$10-15M to continue development of PPL-103 through PoC in human clinical trials (Phase 2a)

Future Capital Requirements: Seeking \$10-15M for Next Phases of Development

Phase 1 Safety and Dose Range (~\$3.5-4M)

- SAD/MAD
- Drug effect studies
 - Human abuse liability
 - Respiratory depression
 - Physical dependence and withdrawal
 - Constipation

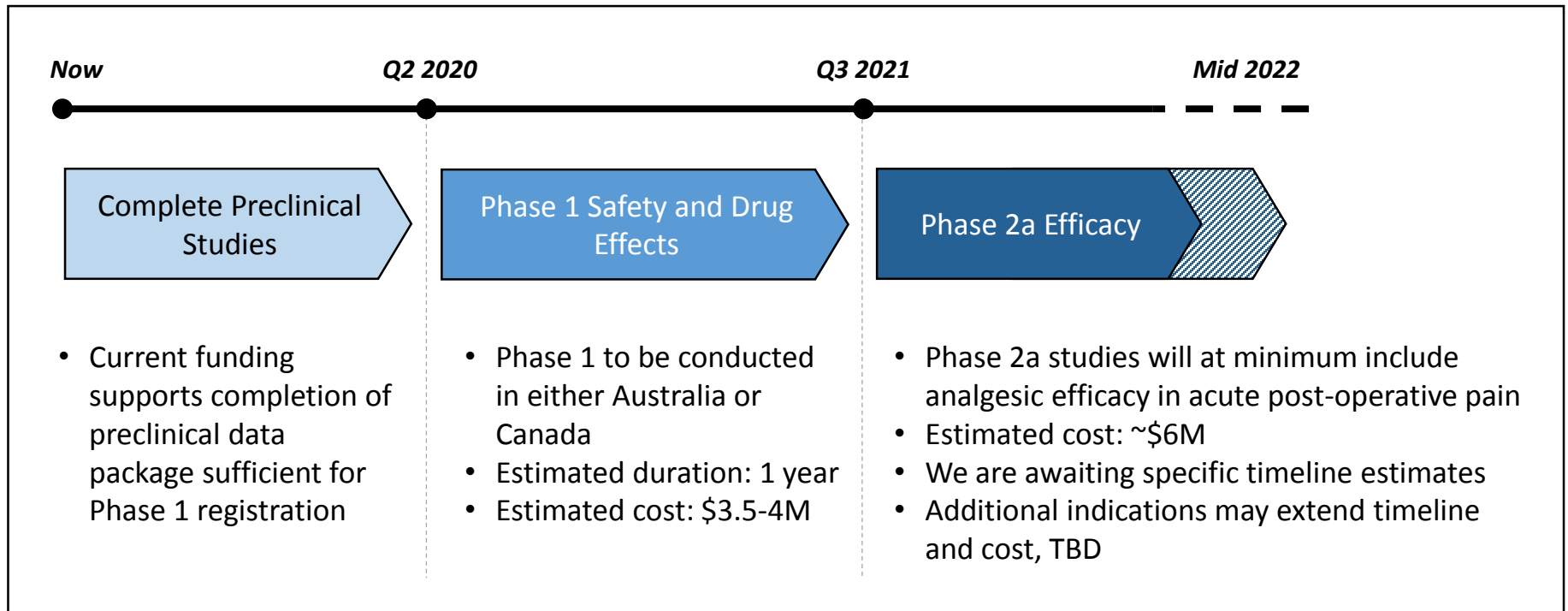
Phase 2a Proof of Concept in Humans

- Analgesic Efficacy (~\$6M)
 - Post-operative acute pain – *primary focus*
 - Visceral pain
 - Inflammatory pain
- Additional indications (cost TBD)
 - Opioid addiction therapy
 - Cocaine addiction therapy
 - Anti-itch

We believe the value of PPL-103 is optimized for pursuing partnership with or acquisition by a larger pharmaceutical company upon positive Phase 2a efficacy data

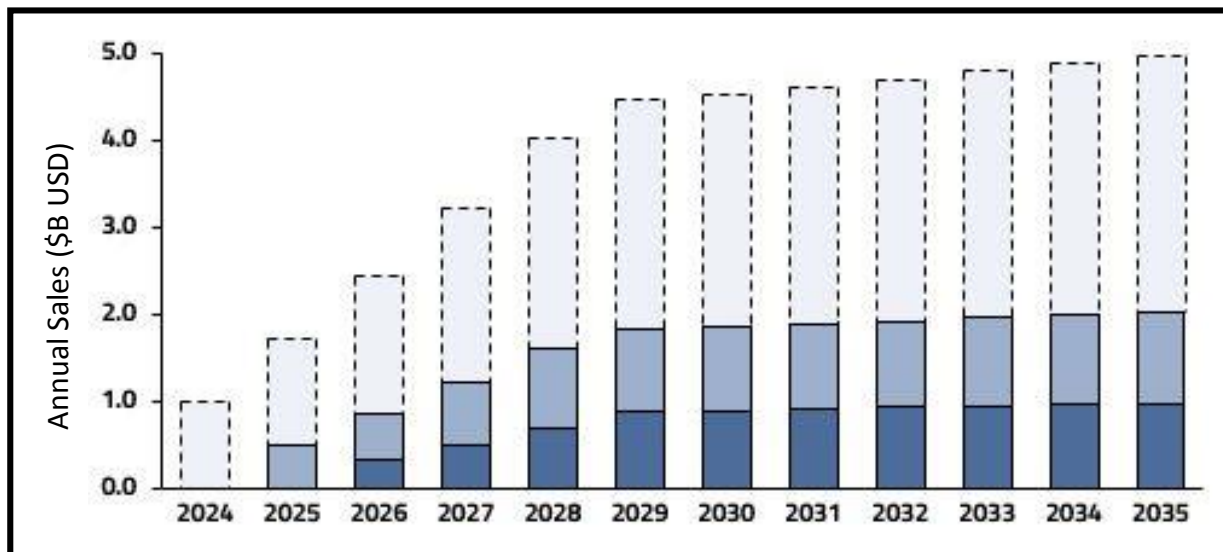
We estimate a ~3 year timeline to Phase 2a Proof of Concept in humans

Clinical Development Timeline



We expect to reach target annual peak sales of ~\$2B by 2029 with U.S. prescription volume capture of only 10%

PPL-103 Annual U.S. Revenue Projections (\$B USD)



Additional Notes

- PPL-103 U.S. Patent lifespan expected through 2035
- There are very few competitive agents in development
 - Mu / Nop compounds show promise but have less supporting data and greater translational risk
- \$2.0B annual sales in U.S. equates to ~4.5M prescriptions annually at 2017 branded opioid pricing
- The introduction of a safe and non-addictive opioid may also increase physician willingness to prescribe, further increasing prescription volumes and sales

Conservative

- 5% Market Penetration in U.S.
- 2026 Launch
- Direct Competitor Launch 2027

Target

- 10% Market Penetration in U.S.
- 2025 Launch
- Direct Competitor Launch 2028

Upside

- 12% Market Penetration in U.S. and rest of global market
- 2024 Launch
- Direct Competitor Launch 2028

Multiple pharmaceutical companies with strategic focus on pain and addiction therapy have expressed interest in PPL-103

- Substantial interest in PPL-103
 - Phoenix has had discussions/diligence with most of the leading pharma companies that have a strategic focus on pain or addiction therapy
 - They have all said that they would be interested in doing a deal (license or acquisition) at some point and they have all asked us to keep them updated on our progress
- Targeting deal development upon Phase 2a PoC
 - Most pharma companies have indicated that they would like to discuss terms after we have entered Phase 1 trials
 - However, our plan is to continue to advance PPL-103 through Phase 1 to Proof of Concept (Phase 2a) in order to position the compound for optimal deal terms

Thank You

For further information, please contact:

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Please visit our website at:

[WWW.PHOENIXPHARMALABS.COM!](http://WWW.PHOENIXPHARMALABS.COM)

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Providing a pathway to potent pain relief without risks of addiction and dangerous side effects

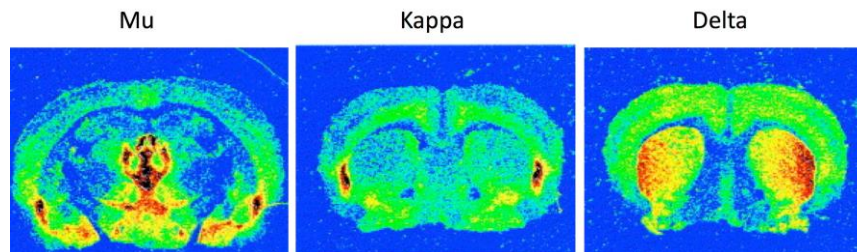
Phoenix PharmaLabs (PPL) is a privately held, preclinical drug discovery company focused on the development and commercialization of new potent, non-addictive treatments for pain as well as treatment of addiction.

Opioids are the most widely prescribed drugs for treatment of moderate to severe pain. They are also the most powerful analgesics for treatment of acute and chronic pain. However, their use is plagued by serious side effects including abuse and addiction, severe withdrawal, constipation, respiratory depression and death from overdose. Millions of Americans are seriously addicted to opioids, and most of them (approximately 80%) initially become addicted after taking prescription opioids. The problem has reached epidemic proportions.

“This is a major public health problem that is getting worse, and getting worse rapidly.” -- CDC

The Opportunity

All of the potent opioid analgesics in use today such as Morphine, Oxycodone, Hydrocodone, Methadone, Fentanyl, etc. bind to the *mu* receptor in the brain and then aggressively agonize that receptor leading to several severe side effects including euphoria (which leads to abuse and addiction) severe withdrawal, constipation, respiratory depression and death from overdose. But there are three primary opioid receptors: *mu*, *kappa* and *delta*. Some *kappa* drugs have been developed, but they are never prescribed because they produce dysphoria. *Delta* is neutral – it does not produce as much analgesic potency as *mu* or *kappa*, but it has no side effects.



The Solution

PPL has developed a novel family of New Molecular Entity (NME) ligands with high binding affinity at all three receptors. These unique ligands have more balanced receptor activity than other opioids, with partial agonist / antagonist activity at mu, somewhat higher, but not full, kappa agonist activity, and moderate delta activity. Thus they derive potent analgesia primarily from mu and kappa, but do not stimulate those receptors so intensely that they trigger the negative side effects of either receptor. This profile results in first-ever opiate analgesics that appear to be non-addicting and free of all significant side effects.

The reason that other opioids are addicting is because they produce a euphoric "high". Without that euphoria, drugs would not be abused and would not be addicting. PPL-103 has clearly demonstrated that it does not produce either euphoria or dysphoria. Research has shown that there is an extremely high correlation between these animal studies and human abuse liability (HAL) studies [1].

Studies of PPL’s drugs have been conducted by prominent scientists at leading institutions including Lou Harris and colleagues at Virginia Commonwealth University (VCU), Jim Woods and colleagues at the University of Michigan, and Larry Toll and colleagues at SRI International Laboratories and Torrey Pines Institute for Molecular Studies. Study results in rodents and monkeys performed by the National Institutes of Health (NIH)/National Institute on Drug Abuse (NIDA), SRI and Torrey Pines demonstrated that PPL-103 is a potent opioid with a profile that is **neither mu nor kappa** -- and is free of the serious side effects of **both**.

Characteristic	Mu Opioids	Kappa Opioids	PPL-103
Significant Self-Administration / CPP (Euphoria)	Yes	No	No
Significant CPA (Dysphoria)	No	Yes	No
Lethal Respiratory Depression at High Dosage	Yes	No	No
Significant Constipation	Yes	No	No
Withdrawal Symptoms	Severe	No	No
Sustains Without Opiate Withdrawal	Yes	No	Yes

Since PPL-103 does not precipitate withdrawal, it also offers very promising use for addiction therapy as a preferred substitute for methadone, buprenorphine and Suboxone, since those drugs are, in and of themselves, addicting opiates that addicts typically have to remain on for life. Recent studies have demonstrated that PPL-103 also has promising potential for cocaine addiction therapy as well.

PPL-103 has been substantially de-risked in animals relative to problems that are likely to occur with opioids. A vast amount of opioid testing data is available concerning the transition of effects of pure opioid compounds from animals to humans. The predictive validity from animals to humans is very high, and thus there is a high level of confidence that this compound will be safe, effective and beneficial for humans.

Future Plans & Funding

The strategic objective of our company is to enter into license agreements with appropriate market leader(s) that have the resources to further develop, commercialize, and maximize the market potential of PPL’s family of drugs. We intend to advance PPL-103 to Proof of Concept (POC) in humans at which point it will be very well positioned for out-licensing. It is possible, however, that we could decide to enter one or more license agreements or an acquisition or an IPO before that point is reached.

We recently received \$3 million in grant funding from the US Army Medical Research and Material Command (USAMRMC) and the NIH that will fund the advancement of PPL-103 into human clinical trials. We are now raising additional funds to advance the drug to POC.

For Further information:

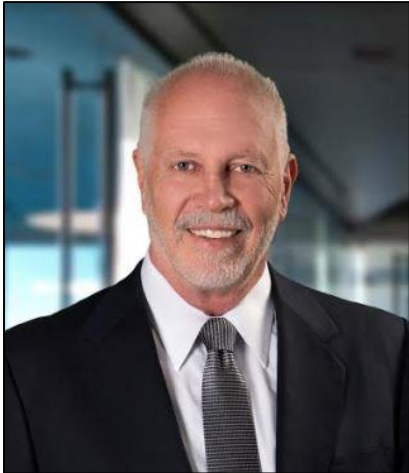
Website: www.phoenixpharmalabs.com
Contact: William Crossman, President and CEO
bill@phoenixpharmalabs.com
860-305-6955

[1] O’Connor EC, Chapman K, Butler P, Mead NM. (2011) The predictive validity of the rat self-administration model for abuse liability. *Neurosci Biobehav Rev* 35:912-938

Management & Directors

William Crossman

President, CEO & Board Member



Mr. Crossman is responsible for the overall management of the Company and the creation, planning and execution of business and financial strategies and corporate development activities, including capital generation.

Crossman is a senior management professional with international and domestic experience as CEO, COO and CFO of enterprises ranging from entrepreneurial start-ups to Fortune 500 level companies. He has a proven track record of successfully commercializing various emerging technologies including manufacturing and industrial systems, computer software, marine bioremediation, nanotechnology and life sciences. Mr. Crossman has assisted numerous early-stage companies to refine business strategies, commercialize new products, raise capital, license technologies, scale revenues and production, and expand into global markets. As CEO of ISOPur Fluid Technologies, Crossman led the company from product introduction to global growth with expanding applications in multiple vertical markets. Important strategic alliances were developed with Siemens, BHP, Atlas Copco, Hess, Sanwa Shoko and others, creating a platform for continued strong growth. The value of the founding shareholders' common stock increased more than tenfold in less than three years under Crossman's leadership. As CFO of Otis Elevator Company – Asia Pacific Operations, Crossman evaluated, negotiated and developed acquisitions, joint ventures and major capital investments in China, Japan, Korea, India, Southeast Asia, and Australia. Mr. Crossman contributed to profit growth of 20% per year and market share gains of 1% per year in this mature multi-billion dollar operation spanning 23 countries, despite aggressive competition from large Asian conglomerates. The joint ventures that he helped developed in China are among the most profitable operations of United Technologies Corp today. Bill holds a BS degree from the U.S. Merchant Marine Academy at Kings Point and a MBA from the Haas School of Business at the University of California – Berkeley.

Management & Directors

John A. Lawson, Ph.D.

Founder, Chairman & Chief Scientific Officer



Dr. Lawson is responsible for the planning of R & D and the supervision and execution of all chemistry activities related to drug discovery and development.

John Lawson is an expert in medicinal and synthetic organic chemistry. As a senior Medicinal Chemist and Project Manager at Stanford Research Institute (SRI International) for 20 years, he headed the Neurochemistry R & D Group with responsibilities for the discovery and development of new compounds in neuroscience area including analgesics, anti-convulsants, anxiolytics, and stroke. While at SRI, Lawson collaborated for ten years with Dr. Toll, Chief Neuropharmacologist and Board Member of Phoenix PharmaLabs (see below), on analgesic drugs under NIH grant funding. During this period, Dr. Lawson discovered the initial class of opioids capable of relieving pain without the typical side-effect problems of morphine-like opioids. After leaving SRI, Lawson assisted in the opening of a synthetic laboratory at SynVax, Inc. for the purpose of developing new drugs related to Nociceptin — a recently discovered brain chemical that modulates pain responses. Two years later, he left SynVax and founded Phoenix PharmaLabs, Inc. (PPL), for the purpose of renewing the development of non-addicting opioid compounds which ultimately resulted in the development of the company's lead compound, PPL-103. John holds a BS degree with Phi Kappa Phi honors from Iowa State University and a Ph.D. from the University of Oregon. He was also a Postdoc. fellow at Syntex Corp.

Management & Directors

Timmy Chou

Vice President, CFO & Board Member



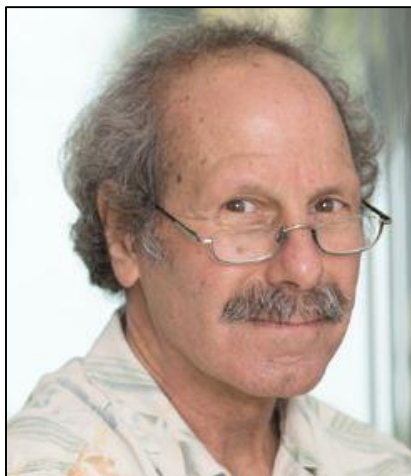
Mr. Chou is responsible for the management of Company finances, corporate governance and treasury matters, including accounting and disbursements as well as the planning and execution of corporate development activities, including capital generation.

Timmy Chou's corporate experience includes serving as a Chief Financial Officer, Controller, and CEO, as well as a management consultant for numerous companies. He is a founding partner of Spectra Consulting Group, where for more than 25 years he has performed consulting on growth issues in emerging businesses, including specialized consulting in strategic planning, cash management, capital structures, dispute mediation, and organizational re-engineering and process development. He is a serial entrepreneur and currently serves as an officer of several operating public and private companies and sits on various Boards as a director. He has participated in architecting numerous capital structures and has developed strategies for development-stage enterprises that have produced significant debt and/or equity investment. Mr. Chou is listed as an affiliate of the Wasatch Venture Network and is a member of the Association for Conflict Resolution and Utah Dispute Resolution. Timmy holds a bachelor's degree from Brigham Young University and has pursued graduate work at the University of Utah.

Management & Directors

Lawrence Toll, Ph.D.

Founder, Chief Neuropharmacologist & Board Member

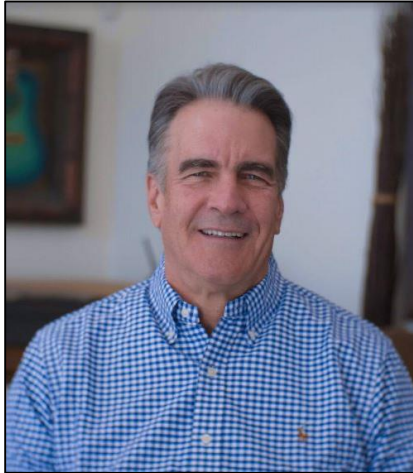


Dr. Toll is currently Professor, Department of Biomedical Sciences, Charles E. Schmidt College of Medicine, Florida Atlantic University. He is also President of the International Narcotics Research Conference. Formerly he was Director of Neuropharmacology, Torrey Pines Institute for Molecular Studies, and prior to that he was Director of the Neuropharmacology Department at SRI International where he conducted basic and translational research in the fields of pain and addiction. An author of more than 130 peer-reviewed scientific papers, he is a recognized expert and leading researcher in the field of neuroscience, particularly in relation to addiction neurobiology and the pharmacology of drugs with potential addiction liability, such as opiates. Dr. Toll is a co-discoverer of the “nociceptin” opioid peptide and was part of the Opiate Research team at SRI that first researched potential non-addicting opioids. Dr. Toll has performed numerous selected assessments of neurochemical drugs for the National Institute on Drug Abuse (NIDA). As part of NIDA’s Opiate and Cocaine Treatment Discovery Programs he tested a very large number of compounds for affinities and activities at the three opioid receptors, 5 dopamine receptors, several 5-HT receptors, PCP receptors and sigma receptors. In conjunction with this project, Dr. Toll and his team published the definitive in vitro profile of opioid- and cocaine-related ligands. His lab has collaborated with many medicinal chemists to characterize the activity of a large number of compounds, including PPL’s compounds. Larry holds a BA degree in chemistry from the University of California, San Diego and a Ph.D. in biological chemistry from the University of California, Los Angeles as well as a Postdoc. in biological chemistry at the University of California, Los Angeles and a Postdoc. in pharmacology at Johns Hopkins University.

Management & Directors

Chris Tew

Vice President and Board Member



Mr. Tew is responsible for participating in the planning and execution of business development strategies and the active management of promotional and public relations activities and relationships as well as capital generation. Mr. Tew brings over 25 years of professional bioscience sales, marketing and business development leadership experience to the company as a sales, marketing and development executive with American Hospital Supply, CooperVision, and Alcon. Throughout his career Mr. Tew championed many successful sales and product initiatives. In addition, Chris co-founded HealthWare Management Company, a healthcare software company, which was sold at a profit to Global Software. Chris holds a BA degree in mass communications from Brigham Young University and completed an executive training program at Stanford University.

Scientific Advisors

Mary Jeanne Kreek, M.D.

Consultant, Addictive Diseases and Therapy

Dr. Kreek is Senior Attending Physician and Patrick E. and Beatrice M. Haggerty Professor, Head of Laboratory of Biology of Addictive Diseases, The Rockefeller University. She is the recipient of numerous professional awards including: Betty Ford Award, Association for Medical Education and Research in Substance Abuse, 1996; Specific Recognition Award, Research in Science of Addiction, Executive Office of the President – Office of National Drug Control Policy 1998; R. Brinkley Smithers Distinguished Scientist Award, American Society of Addiction Medicine, 1999; Nathan B. Eddy Memorial Award for Life-time Excellence in Drug Abuse Research, College on Problems of Drug Dependence, 1999; Fellow, New York Academy of Sciences, 2000; Columbia University College of Physicians and Surgeons Alumni Association – Gold Medal for Distinguished Achievements in Academic Medicine, 2004; Marian W. Fischman Memorial Lectureship Award, College on Problems of Drug Dependence, 2005; President, International Narcotics Research Conference 2002-2006. Dr Kreek holds a BA in Chemistry from Wellesley College and an MD from Columbia College of Physicians and Surgeons, Sigma Xi, Phi Beta Kappa: Durant Scholar.

Daniel E. Levy, Ph.D.

Consultant, Chemical Synthesis and MFG Scale-Up

Dr. Levy is an experienced organic/medicinal chemist having contributed to the design of novel therapeutic agents targeting cardiovascular, cancer, inflammatory and CNS disorders. In his almost 30 years in industry, Dr. Levy led interdisciplinary teams focused on kinase inhibitors, GPCR antagonists, matrix metalloproteinase inhibitors and cell adhesion molecules. His work is documented in over 30 peer-reviewed publications and over 11 issued/published United States patents. Dr. Levy is Founder and Principal Consultant of DEL BioPharma LLC, through which, he provides CMC services covering medicinal chemistry, API manufacturing and formulation development. Most recently Dr. Levy was the Vice President of Manufacturing at Censa Pharmaceuticals and the Director of Synthetic Chemistry at Intradigm Corporation. He is author and editor of three books covering aspects of mechanistic organic chemistry and carbohydrate chemistry. Dr. Levy received his academic degrees from the University of California – Berkeley (B.S., 1987) and the Massachusetts Institute of Technology (Ph.D., 1992).

Scientific Advisors

Shayne Gad, Ph.D.

Consultant, Toxicology and Regulatory Affairs

Dr. Gad is Principal, Gad Consulting Services, a twenty year old consulting firm with over 300 pharmaceutical companies as clients. He has more than 35 years of broad-based experience in toxicology, drug development, statistics and risk assessment and has authored or edited 44 published books in these fields. He is the recipient of the American College of Toxicology Lifetime Contribution Award. He has direct involvement in the preparation of INDs (96 successful to date), NDA, PLA, ANDA, 510(k), IDE, CTD, clinical data bases for Phase I and II studies, and PMAs. He has consulted for FDA, EPA AND NIH, and has trained reviewers and been an expert witness for the FDA. Shayne holds two BS degrees from Whittier College in Chemistry and Biology, and a Ph.D. in Pharmacology / Toxicology from the University of Texas DABT, ATS.

Gantt Galloway, Pharm.D.

Consultant, Clinical Trial Design

Dr. Galloway has over 30 years of experience designing and supervising Phase I, II, and III clinical trials. His research positions have included Senior Scientist of the Addiction & Pharmacology Research Laboratory at the California Pacific Medical Center Research Institute and Senior Research Scientist at Friends Research Institute. He is a member of the faculty of the University of California, San Francisco and has chaired Data and Safety Monitoring and Institutional Review Boards. Dr. Galloway has served on advisory and review committees for the Substance Abuse and Mental Health Services Agency, the National Institute on Alcoholism and Alcohol Abuse, and the National Institute on Drug Abuse. In addition to his research activities, Dr. Galloway served as Executive Director of New Leaf Treatment Center, a clinic providing treatment for addiction and for pain. Dr. Galloway holds a Pharm.D. from the University of California, San Francisco.

Scientific Advisors

Mei-Chuan (Holden) Ko, Ph.D.

Consultant, NHP Studies

Dr. Ko is Professor, Department of Physiology & Pharmacology, Wake Forest University School of Medicine. He has a 23-year history of research using rodents and nonhuman primates with a record of successful and productive research projects in areas of opioids and substance abuse. As PI or co-investigator on many university-, industry-, and NIH-funded grants, Professor Ko has studied approximately 60 newly developed experimental compounds and laid the groundwork for the proposed research by developing various behavioral and physiological measurements in rodents and monkeys following systemic and intrathecal administration of drugs. Dr. Ko has authored dozens of peer-reviewed scientific papers and is the recipient of several professional awards including: CPDD Early Career Investigator Award, 2002; Wyeth-Ayerst Young Psychopharmacologist Award, 2002 and Research Excellence Award, Wake Forest University School of Medicine, 2014-2015. Dr. Ko holds a Ph.D. in biopsychology as well as a Postdoc. in anesthesiology/pharmacology from the University of Michigan.

Addiction and death from opioid abuse is “a major public health problem that is getting worse rapidly”

Opioids are the most widely prescribed drugs for treatment of moderate to severe pain. They are also the most powerful analgesics for treatment of acute and chronic pain. Whether after surgery, or on a battlefield, or simply after a root canal, opiates are prescribed in rapidly increasing numbers. In 1990 there were 78 million prescriptions written for opiate medications in the US; by 2010 this value nearly tripled to 210 million prescription [1]. However, their use is plagued by serious side effects, including abuse and addiction, constipation, respiratory depression, and death from overdose. In the US, more than 2 million people are addicted to opioids – and this number is increasing steadily [2]. In 2011, ~500,000 people were sent to the emergency room for treatment of opioid-related problems. Abuse of prescription drugs is highest among young adults aged 18 to 25, with 5.9% reporting nonmedical use in a month [2].

From a CDC report in 2011: US death rates have declined over the past ten years for all major causes of death *except for death from prescription opioid abuse*. The CDC has declared this to be “a major public health problem that is getting worse, and getting worse rapidly” [3]. A follow-up report in 2012 stated that the epidemic of overdoses of opioid pain relievers (OPRs) has continued to worsen. OPR deaths represent nearly 75% of all prescription drug overdose deaths. Drug overdose deaths have now exceeded deaths from motor vehicles as the #1 cause of accidental death in the US [4].

While alternatives to opioids exist, these are largely inadequate for treating the kinds of pain treated by opioids. As a considerable amount of pain is due to inflammation, both steroids and non-steroidal anti-inflammatory drugs (NSAIDs) attenuate the pain at its source by reducing inflammation. These types of drugs are successful for mild pain, and some powerful anti-inflammatory compounds are effective for moderate pain. They are generally safer than opiates because they lack the rewarding aspects that cause dependence and addiction. However, they are generally ineffective for severe pain, such as is incurred in combat and military training. Moreover, NSAIDs have their own side effects, leading to increased bleeding and stomach problems: the last thing a patient would want after a battlefield injury would be something that prevents clotting. This leaves opiates as the only currently acceptable option for treatment of injuries on site and they are still the most highly used treatment once removed from the battlefield, often as part of a multi-modal pain treatment plan.

Opioids remain extremely problematic because of the poor outcomes associated with their side effects. But it should be recognized that all of the leading opioid analgesics on the market today are **mu opioids** – i.e. opioids acting at the **mu opioid receptor**. The mu receptor produces euphoria, and it is that euphoric “high” that leads to abuse and addiction. Furthermore, withdrawal from mu opioids induces very severe physical and psychological symptoms that often lead to relapse. Without that euphoric high and severe withdrawal, the drugs would not be abused and would not be addicting. Mu opioids also create other serious side effects including constipation and respiratory depression. Mu-opioid side effects and the benefits of non-mu opioid analgesia are discussed in detail below.

Mu opioid receptor agonists are the current standard for opioid pain relief

Opiates treat pain by blocking the pain signal from reaching the pain centers of the brain, either at the level of the spinal cord or in the brain directly. There are four receptors in the opioid receptor family: mu (μ), delta (δ), kappa (κ), and NOP, where systemic administration of small molecule agonists of the first three receptors mediate an analgesic response [5]. Historically, most opiate analgesics have been mu agonists, due to their potent analgesic activity. These include the natural product morphine, short acting potent analgesics such as fentanyl, and long-lasting compounds such as methadone. More recently the orally active powerful mu agonists oxycodone and hydrocodone have dominated the field of prescription opiates. However, all mu agonists induce significant side effects, including euphoric reward, which leads to abuse and addiction liability, severe physical withdrawal symptoms, constipation, and respiratory depression, which can lead to death from overdose.

Other opioid receptors have been examined in detail, but have not been found to be suitable for analgesic

therapy. High affinity delta agonists, such as SNC80, have a much more restricted analgesic profile, often cause convulsions and have not yet proven successful clinically [6,7] Delta agonists, however, do have significant antidepressant activity [8], a property that could be beneficial in a compound that has activity at each of the opiate receptors. Kappa agonists have potent antinociceptive activity in many animal models however they have proven to be dysphoric and psychotomimetic in animal models and in people [9-11], and therefore have never been approved for use in man. Consequently, mu full or partial agonists, with or without some additional component (e.g. acetaminophen), are the analgesics of choice. However, as noted, these agents have the most severe side effects and are the most addicting, leading to the current epidemic of prescription drug dependence.

Mu opioid receptor agonists cause euphoria and are addictive; kappa receptor agonists cause dysphoria

Opiate pharmacology is very mature, with decades of research from pharmaceutical companies and academia. Because of the known problems with mu opiates, researchers have been attempting to produce analogs with reduced side effects for over 100 years, well before the opiate receptors were discovered or subtypes were identified. In fact, it was the pharmacological actions of opiate analogs that led Martin and colleagues to classify opiate receptors into subtypes [12].

Once opiate receptor subtypes were identified and could be examined independently for both binding affinity and functional activity, researchers attempted to modify the receptor binding profiles and efficacy of novel ligands with the hope of reducing side effects. This effort resulted in the synthesis and evaluation of “mixed agonist/antagonists”, such as nalorphine (a kappa agonist and mu antagonist); mu/kappa agonists, such as nalbuphine; partial mu agonists, such as buprenorphine; and kappa agonists such as spiradoline. Each of these compounds has analgesic activity in animal models and people, and each has their own problems [13]. Table 1 shows the major beneficial and detrimental actions of mu, kappa, and delta opioid agonists.

	Analgesia	Reward	GI Motility	Respiration	Activity	Renal	Withdrawal
Mu	Potent	Euphoria	Constipating	Respiratory depressant	Species dependent	Anti-diuretic	Severe
Kappa	Potent	Dysphoria	Little effect	No effect	Sedative	Diuretic	Mild
Delta	Mild to moderate	Mild reward	Constipating	No effect	Increase	Diuretic	Unknown

Table 1: Side effect profile of mu, kappa and delta agonists

Morphine and other **mu opiates**, although potent analgesics, cause severe constipation, respiratory depression (sometimes causing death by overdose), and of course are euphoric or rewarding, leading to severe abuse liability and addiction. In addition, once dependent, withdrawal is very severe, often preventing abstinence. Mu antagonists (e.g. naltrexone or nalorphine) also induce withdrawal if the patient or addict is dependent on opiates. **Kappa agonists** (e.g. nalorphine and spiradoline) can also have potent antinociceptive activity, however they have very little effect on GI motility or respiration, making these compounds much safer than mu agonists. In addition, once dependent, the abstinence syndrome is very mild compared to mu agonists. Not only do kappa agonists not induce euphoria, in fact they induce dysphoria and often psychotomimetic activity. For this reason, kappa agonists have not been successful clinical compounds [14,15]. If one could discover a kappa agonist without the negative psychological aspects, these could be ideal analgesics.

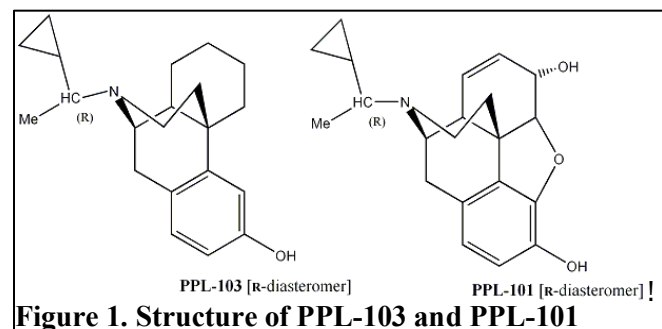


Figure 1. Structure of PPL-103 and PPL-101

It has long been recognized that **mu partial agonists** have reduced side effects. In fact, the partial mu agonist buprenorphine is quite a good drug. It has a ceiling effect on both GI motility and respiratory depression, thereby reducing its side effect profile and increasing its therapeutic index [16]. It also has reduced physical dependence [17,18]. Nevertheless, it has sufficient mu

agonist activity to be addicting in people, and as such is a Schedule III narcotic. By analogy, a kappa partial agonist would likely have reduced side effects as well, in this case less sedation and dysphoria. Furthermore, a **kappa partial agonist with some small amount of mu efficacy might have analgesic activity with the euphoria/dysphoria balanced out due to activation of both receptors.**

Phoenix is developing a better alternative: PPL-103 – a mu/delta/kappa partial agonist/antagonist

In order to develop an opiate with reduced side effects, many investigators and pharmaceutical companies conducted structure activity relationship (SAR) studies on morphine and analogs. Early on it was determined that modification of the N-substituent of morphine could change the compound from an agonist into an antagonist. N-allyl or N-cyclopropylmethyl (N-CPM) substitution would lower efficacy at mu receptors and could lead to either agonist/antagonists such as nalorphine or antagonists such as naloxone. Several years later, when the opioid receptors were identified, it was determined that N-allyl and N-CPM also changed the binding profile, increasing binding affinity to the kappa receptor while maintaining mu binding [19].

Compound	Mu Ki (nM)	Delta Ki (nM)	Kappa Ki (nM)
DAMGO	0.88 ± 0.07	300.0 ± 58.6	305.5 ± 46
DPDPE	503.6 ± 10.0	1.59 ± 0.08	>10,000
U69593	1,145 ± 335	>10,000	1.6 ± 0.26
morphine	1.1 ± 0.05	140.0 ± 1.5	46.9 ± 14.5
buprenorphine	1.5 ± 0.8	4.5 ± 0.4	0.8 ± 0.05
PPL-101	0.35 ± 0.04	3.97 ± 1.41	0.43 ± 0.11
PPL-103	0.36 ± 0.11	2.47 ± 0.105	0.29 ± 0.03

Table 2: Opioid receptor binding affinities of PPL-103 (α -methyl-CPM-morphinan), PPL-101 (D1) and standard opioids.

Compound	Mu		Delta		Kappa	
	EC ₅₀ (nM)	% Stimulation	EC ₅₀ (nM)	% Stimulation	EC ₅₀ (nM)	% Stimulation
DAMGO	13.7 ± 5.2	100	>10,000		>10,00	
DPDPE	>10,000		1.3 ± 0.5	100	>10,000	
U69593	>10,000		>10,000		78.4 ± 8.8	100
morphine	16.0±1.0	97.6±1.0	412±12	78.1±0.9	575±81	24.9±1.9
buprenorphine	2.3 ± 1.7	19 ± 05	flat		flat	
PPL-101	0.3±0.09	12.2±2.9	39.6±6.30	22.4±5.83	15.2±2.5	62.6±0.33
PPL-103	4.30±2.1	22.6±0.05	9.01±2.64	39.8±3.9	2.99±0.92	41.7±5.0

Table 3: Functional activities of PPL-103, PPL-101 and standard opioids using the [³⁵S]GTP γ S binding assay

While studying the importance of the N-substituent in morphine analogs for binding affinity and functional activity, Dr. John Lawson, founder of Phoenix PharmaLabs, introduced a new chiral center in morphine analogs by inserting a methyl group onto the alpha carbon in N-CPM morphine (**Figure 1**). This insertion restricted the rotation of the N-substituent and produced two diastereomers of α -methyl-CPM morphine: D1 (now named PPL-101) and D2 [20]. It turned out that PPL-101 has a favored conformation, high affinity for mu, delta, and kappa opioid receptors (**Table 2**), very weak partial agonist activity at mu receptors, with slightly higher efficacy at delta and kappa receptors [21] (**Table 3**). It has been tested many times in mice, rats, and monkeys for antinociceptive activity, addiction liability and other side effects and has demonstrated a particularly promising profile [22-25]. However, pharmaceutical companies

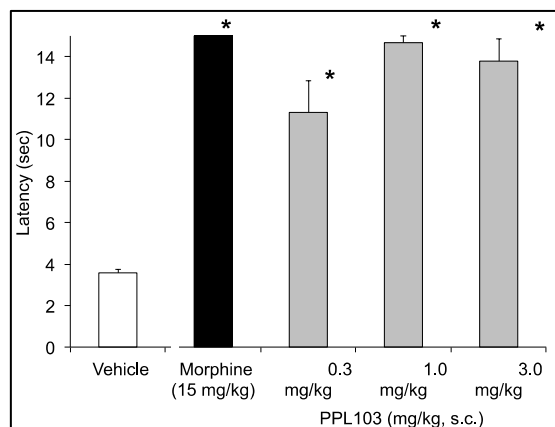


Figure 2: PPL-103 has potent anti-nociceptive activity in the tail flick assay in mice. n=10 mice per group. *p<0.05

have not been interested in further exploring the clinical utility of PPL-101, as it is now off patent. Accordingly, we continued SAR studies and came up with a set of new compounds, including PPL-103 (α -methyl-CPM-morphinan), a very close structural analog of PPL-101. As seen in **Tables 2** and 3, PPL-103 has high affinity at each of the opioid receptors and has partial agonist activity at each receptor [21]. As presented below, this profile yields a potent analgesic (three times more potent than PPL-101 and ~10 times more potent than morphine in the tail flick assay), with greatly reduced side effects and a greatly diminished risk of abuse liability, but without dysphoria.

PPL-103 is a potent analgesic with a reduced reward and side effect profile

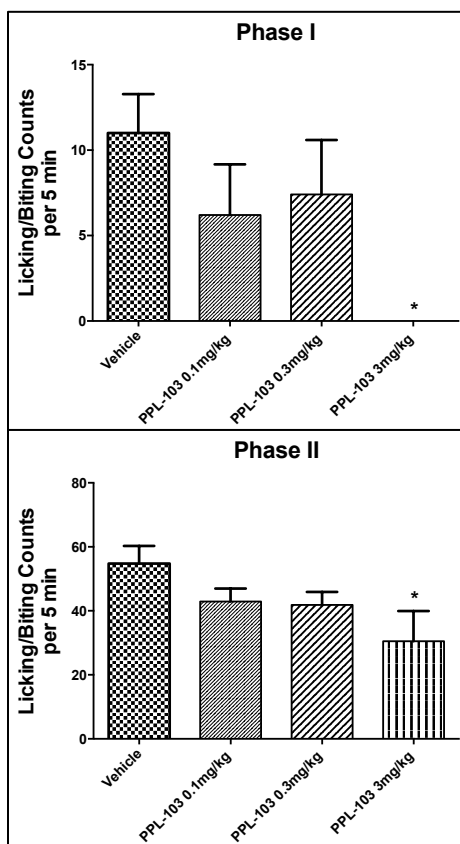


Figure 3. PPL-103 reduces pain in the formalin assay in rats. PPL-103 was administered orally. Formalin was administered to the paw 30 min after PPL-103 and painful responses were quantified over the following hour with phase I representing the first 10 min and Phase II the following 50 min.

spinal nerve ligated rats. We have demonstrated this to be equivalent to a 10mg/kg dose of morphine, in the same pain model [27]. As expected for a kappa agonist, PPL-103 was very effective in blocking pain in the acetic acid writhing test, a model of visceral pain. With an ED₅₀ of approximately 0.1 mg/kg, PPL-103 was nearly 10 times more potent than morphine. (**Figure 5**).

When tested for side effects, PPL-103 was significantly different than morphine, exhibiting the milder and more tolerable side effect profile more characteristic of kappa agonists, but without the dysphoria.

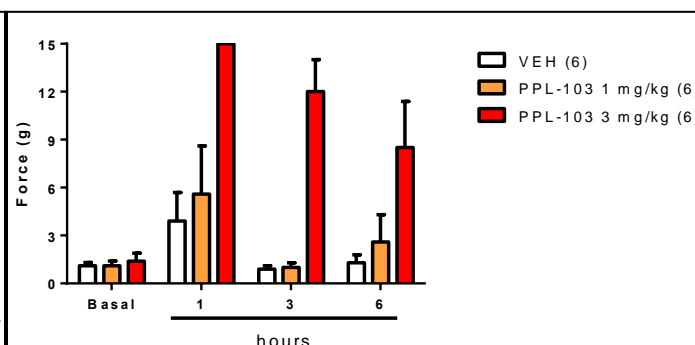


Figure 4. PPL-103 has antiallodynic activity in spinal nerve ligated rats. Von Frey filaments were used to measure allodynia in SNL rats. Measurements were taken 1, 3, and 6 h after i.p. PPL-103 administration.

2.0 mg/kg). When tested in the presence of selective antagonists, PPL-103 antinociceptive activity was attenuated by both nor-BNI (kappa selective) and β -FNA (mu selective), indicating that analgesic activity seems to be mediated to some extent by both receptors. PPL-103 also has antinociceptive and anti-allodynic activity in other rodent models. In the formalin test, a measure of inflammatory pain, PPL-103 had an ED₅₀ of approximately 3 mg/kg when administered orally (**Figure 3**). Even when administered orally, PPL-103 was almost as effective as morphine, which has an ED₅₀ of 2.2 mg/kg when administered s.c. [26]. PPL-103 is also effective in chronic neuropathic pain models. As demonstrated in **Figure 4**, PPL-103 was fully effective at 3 mg/kg when inhibiting mechanical allodynia in

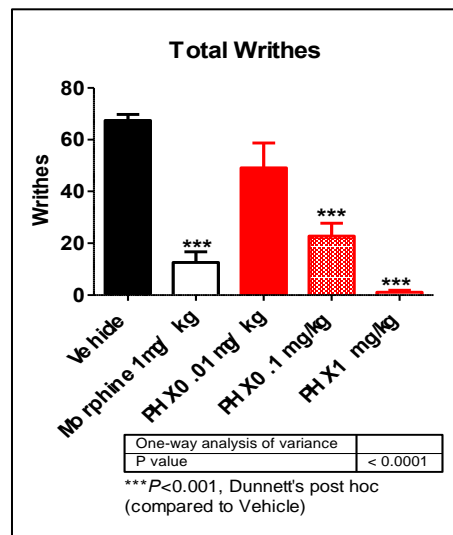


Figure 5. PPL-103 is very effective in the acetic acid writhing model of visceral pain after s.c. administration. Data shows total writches in 20 min after i.p. injection of 0.9% acetic acid.

PPL-103 has been determined to be a very potent analgesic in a **Tail Flick** test in mice, administered s.c. 20-60 minutes before application of radiant heat to the tail. It has exhibited an ED₅₀ of less than 0.3 mg/kg (**Figure 2**), which is 10 times more potent than morphine (ED₅₀ =

Constipation was quantified by measuring the rate that charcoal passes through the intestines. We have demonstrated that PPL-103 does not induce any decrease in the rate of charcoal transport through the intestines of mice at doses up to 50 mg/kg (250x its ED₅₀ in the tail flick assay), and induces only a modest decrease at doses up to 70 mg/kg (350x its ED₅₀ dose). By comparison, morphine caused a greater than 50% decrease at 10 mg/kg, only 5 times its ED₅₀ in tail flick (**Figure 6**).

Respiratory Depression is one of the most severe side effects associated with morphine and other mu opioid receptor agonists; it is the leading cause of opioid overdose death. This side effect was measured in mice in the Comprehensive Lab Animal Monitoring System (CLAMS) for mice (n=10/group), as described in the legend to **Figure 7**. PPL-103 caused only a 25% decrease in respiratory depression at up to 30 mg/kg (150 times its tail flick ED₅₀) and was not lethal even at 70 mg/kg (350 times its ED₅₀ dose) (**Figure 7**).

When **Locomotor Activity** was measured using CLAMS, PPL-103 induced a 50% decrease at doses of 1mg/kg, approximately 5 times its analgesic dose (**Figure 8**). This is in contrast to morphine, which increases locomotor activity in mice at analgesic doses. As a decrease in locomotion is mediated by kappa receptor activity [28,29], these assays demonstrate the predominance of this receptor in PPL-103's activity and side effect profile.

PPL-103 was also tested in mice to determine whether it would induce a **Conditioned Place Preference or Aversion (CPP or CPA)**. The CPP paradigm has been used to measure the rewarding as well as the aversive properties of drugs of abuse. The CPP paradigm measures the incentive motivational properties of stimuli that become associated with drug effects through classical conditioning. The drug is administered in a distinct environment. In this case, daily injections for 6 consecutive days, 3 with drug and 3 with vehicle, while being confined for 15 minutes to a drug-paired or vehicle-paired compartment of the CPP chamber. On the seventh day, the animals are allowed free access to both compartments and the time spent in each compartment is determined. After several pairings, the environment becomes associated with the effects of the drug, thereby acquiring incentive-motivational properties. Thus, the environment becomes a cue eliciting approach (*i.e.* CPP) or avoidance (*i.e.* CPA), depending on whether rewarding or aversive properties of the drug have been conditioned. The CPP paradigm offers several advantages including: (1) Both rewarding and aversive properties of drugs can be assessed using this procedure; (2) other behavioral measures such as locomotor activity can be assessed following acute and repeated drug administration; (3) nonspecific effects of the drug on motor and sensory systems do not influence the behavioral measure because

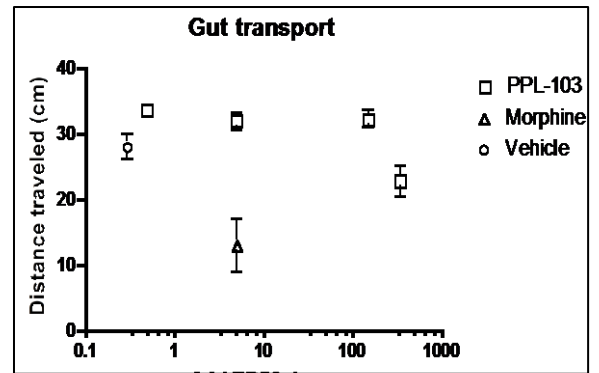


Figure 6. PPL-103 has no effect on intestinal transport. Transport was determined in mice (n=10) by measuring the distance charcoal pellets travelled in 1 h after oral administration. Results are presented in fold ED₅₀ dose, based on an ED₅₀ of 0.2 mg/kg for PPL-103 and 2.0 mg/kg in the tail flick assay.

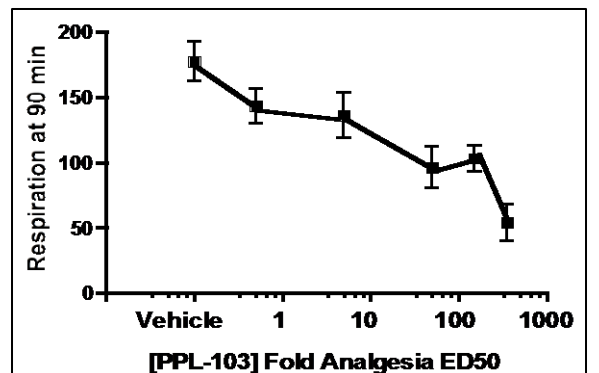


Figure 7. Effect of PPL-103 on respiration. Respiration was measured for 90 min after administration of PPL-103 in mice (n=10/group) using a CLAMS. Oxymax/CLAMS can simultaneously measure and record the following parameters: drinking volume, drinking licks, animal locomotive activity, diuresis, and respiration.

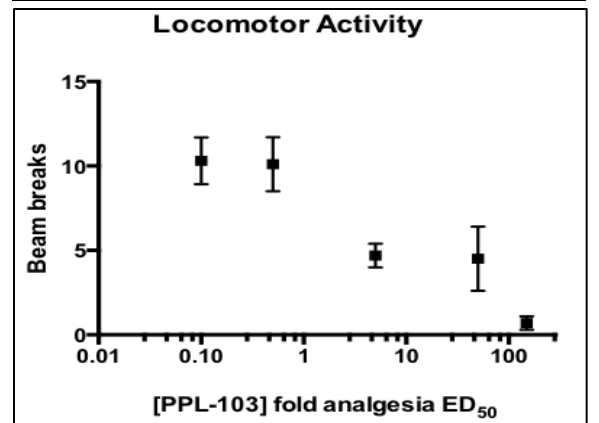


Figure 8. Effect of PPL-103 on locomotor activity in mice. Locomotor activity was determined using the CLAMS system, as described in the legend to Figure 7.

animals are tested in a drug-free state; (4) this method allows for controlled drug doses, whereas with the self-administration paradigm the dose administered is dependent on the animal's rate of responding [30-33]. In this paradigm rewarding substances such as morphine, heroin, cocaine, nicotine, amphetamines and alcohol all induce a CPP, while aversive or dysphoric substances, such as the selective kappa agonist U50,488 induce a CPA.

As expected for mu agonists, morphine elicited significant CPP at 15mg/kg (Figure 9). On the other hand, PPL-103 was expected to elicit CPA based on the apparent kappa-mediated actions described above. However, at each dose of PPL-103 tested, the treated animals spent time in the drug-paired compartment that was not significantly different than either vehicle or morphine. This result indicates that PPL-103 did not have a significant CPP in mice, though with additional numbers of mice significant differences between vehicle, PPL-103 and morphine might be determined. In any case, these studies indicate that **PPL-103 has less reward than morphine but is clearly not dysphoric like kappa agonists.**

PPL-103 was also tested in the **self-administration paradigm in rats.** This assay is the gold standard for determining whether a compound is likely to be self-

administered. **Research has shown that this study has a very high correlation to Human Abuse Liability (HAL) studies and other indications of the potential for abuse and addiction in humans [34].** In this experiment, rats pressed a lever which would deliver a dose of morphine through a jugular catheter using a fixed ration-1 (FR-1) schedule, meaning the rat would receive a single dose of morphine for each active lever press. After being trained to press for morphine, rats were switched to PPL-103 at 2 doses, both of which would be super-analgesic doses compared to morphine (due to the higher potency of PPL-103). As seen in Figure 10, when morphine was substituted with PPL-103, the rats did not press to a greater extent than saline. Rats were then tested on a progressive ratio schedule. In this experiment, the rats must press progressively more times to receive a reward. This measures motivation to work for the reward. In this experiment, as with the FR schedule, rats pressed for PPL-103 in a manner similar to saline. These studies clearly demonstrate that despite a trend toward reward in the CPP assay, rats were not interested in self-administering PPL-103. Based on these studies,

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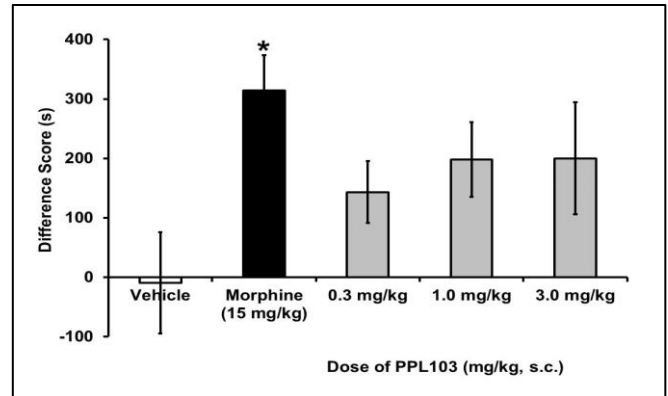


Figure 9. PPL-103 did not induce a significant CPP in mice (n=8), nor was it significantly different than morphine. Unlike morphine, PPL-103 induced a decrease in activity. *P<0.05, significantly different than vehicle control. +, significantly different than day 1 injection.

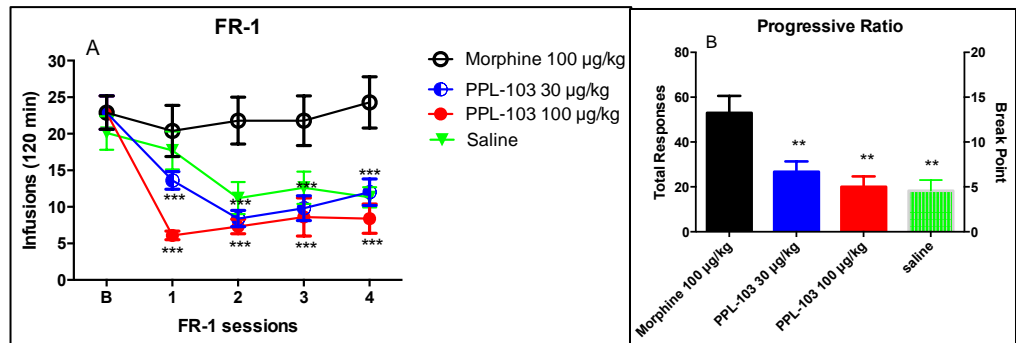


Figure 10. PPL-103 is not self-administered in rats. In both (A) Fixed and (B) Progressive ratio schedules, self-administration of PPL-103 was significantly different than morphine and similar to saline. **p<0.01, ***p<0.001

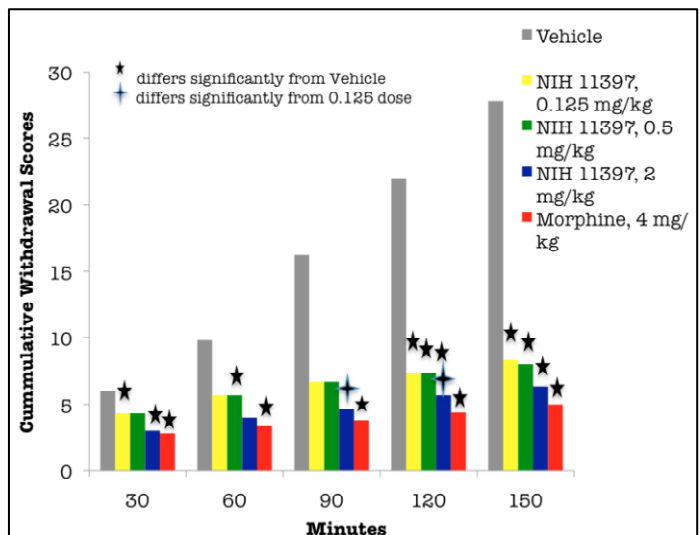


Figure 11. PPL-103 completely substitutes for morphine in the single dose suppression test in rhesus monkeys. Each dose blocked morphine withdrawal signs for 6-9 h. n=3.

there is a high level of confidence that PPL-103 will not be abused in people, but at the same time patients will be compliant because it is not aversive.

Finally, PPL-103 was tested in the **Single Dose Suppression assay** in monkeys (**Figure 11**). In this assay, PPL-103 was tested for its ability to block withdrawal signs in morphine-dependent rhesus monkeys n=3. In this test, PPL-103 substituted completely for morphine in doses ranging from 0.125 to 2.0 mg/kg, completely blocking morphine withdrawal for 6-9 h. It was also noted in these studies conducted by the Committee for Problems on Drug Dependence (CPDD) that PPL-103 induced an overt behavioral syndrome typically manifested in rhesus monkeys by selective kappa-opioid receptor agonists such as enadoline with kappa-like actions including sedation, ptosis and salivation at the higher doses. To quote the report: "Finally, it should be noted that kappa-opioid receptor agonists do not substitute for morphine in the SDS test." That is to say that PPL-103 is very unusual in that it has mostly kappa-like actions, but still can substitute for morphine in the SDS assay. Because of these unusual properties, PPL-103 also offers very promising use for addiction therapy as a preferred substitute for methadone and buprenorphine, since those drugs are, in and of themselves, addicting opiates.

PPL-103 as a cocaine abuse medication

It is known that the kappa receptor system is upregulated with chronic drug treatment, be it opiate, cocaine, or alcohol. As discussed previously, kappa receptor activation leads to stress and dysphoria. Because the kappa system is upregulated, the endogenous agonist dynorphin increases stress and anhedonia, inducing addicts to maintain drug levels to ward off withdrawal. A kappa partial agonist would be expected to reduce levels of stress to more basal levels without inhibiting the kappa system altogether and attenuate the actions of dynorphin upon withdrawal of the drug. This could be successful if the kappa agonist was not dysphoric in itself. A partial agonist would have less dysphoria, and a compound like PPL-103 that is a kappa partial agonist with a small amount of mu activity, as we have demonstrated, is apparently not dysphoric. The value of a kappa opioid receptor partial agonist as a drug abuse medication has been proposed and explained in detail by our consultant Dr. Mary Jeanne Kreek and colleagues [36].

As seen in **Figure 12**, PPL-103 reduces cocaine self-administration in both fixed ratio (FR-1) and progressive ratio schedules of reinforcement. Furthermore, it works better on long access (6 h) rather than short access (1h) sessions. Long access self-administration is considered to be a model of dependent animals. Perhaps more importantly, PPL-103, is very effective, at low doses, at blocking cocaine-prime induced reinstatement of cocaine seeking (**Figure 13**). PPL-103 was also effective in blocking cue-induced reinstatement, but it required 1.0 mg/kg for that effect (data not shown). These data clearly demonstrate that, in addition to great potential as an analgesic with very low abuse liability, PPL-103 has potential as the first cocaine abuse medication. Studies are ongoing to determine whether PPL-103 has potential as an opioid abuse medication.

PPL-103 shows favorable preliminary pharmacokinetic and safety properties

Phoenix PharmaLabs has contracted additional studies to further

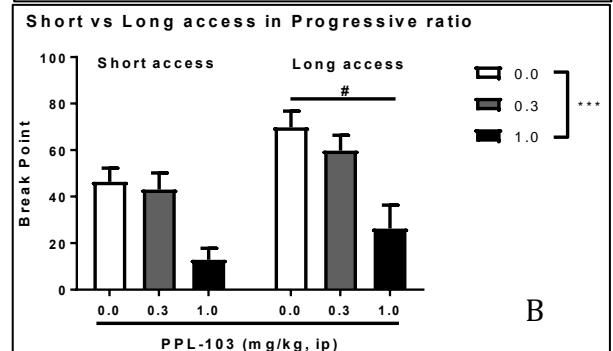
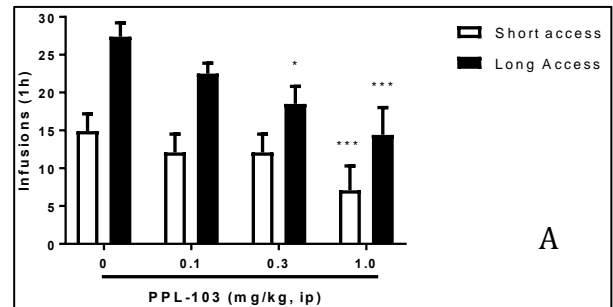


Figure 12. Effect of PPL-103 on A. Fixed ratio and B. progressive ratio cocaine self-administration. In fixed ratio and progressive ratio, PPL-103 is more effective in reducing cocaine self-administration in long-access animals. *p<0.05, ***p<0.001.

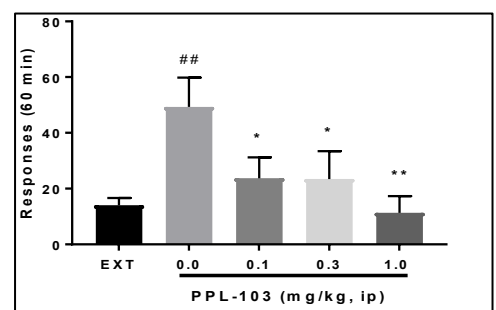


Figure 13. Effect of PPL-103 on cocaine-prime induced reinstatement. At very low doses PPL-103 blocks cocaine reinstatement. *p<0.05, **p<0.01, different than vehicle. ## p<0.01, different than extinction.

examine some pharmacokinetic and safety aspects of PPL-103. Although unstable in rat microsomes, PPL-103 was very stable in human liver microsomes, with a half-life of 173 minutes. PPL-103 was found to have low to moderate plasma protein binding with 58.8% and 75% protein bound in rat and human plasma, respectively. It had very little inhibition of cytochrome P450 (CYP), with an IC₅₀ of greater than 50µM for CYP 3A4 and 1.9µM for CYP 2D6. PPL-103 was found to be highly permeable in the CaCo2 assay (greater than 10⁻⁶ cm/s), indicating oral availability, however it was not a substrate for P Glycoprotein, with an efflux ratio of less than 3.

Pharmacokinetic parameters were studied in rats and monkeys. Although it had relatively low oral availability in rats, probably due to high IV clearance, consistent with instability in rat liver microsomes, PPL-103 had excellent oral availability in monkeys. It had a C_{max} of 70.8ng/ml (230nM), occurring from 2-8h post oral administration of 5mg/kg PPL-103. Half-life at this very high dose was approximately 8h. This high dose induced sedation and a decrease in body temperature in the monkeys.

In a preliminary safety evaluation, PPL-103 was found to be a poor inhibitor of hERG channel with an IC₅₀ of 2.8 µM, indicating that, based upon the C_{max}, it is unlikely to induce a cardiac event in individuals with long QT syndrome at analgesic doses.

In summary, these data suggest that: (1) PPL-103 will get into the brain after oral administration, (2) it has a long half-life, (3) it does not inhibit two important CYP enzymes, and (4) it does not inhibit hERG until reaching high concentrations.

Impact

Taken together, these *in vitro* pharmacology and behavioral studies indicate that PPL-103 is a kappa and mu partial agonist with potent analgesic activity that appears to be mediated by both kappa and mu opioid receptors. Side effects appear to be kappa-mediated, with little to no constipation or respiratory depression. In the CPP/CPA study in mice together with the self-administration study in rats, PPL-103 demonstrated that it produces little or no euphoria, but nevertheless is not dysphoric like other kappa agonists. Despite the kappa mediated actions, PPL-103 substitutes for morphine and blocks morphine withdrawal, suggesting that it could be given to morphine-naïve or morphine-dependent patients without inducing withdrawal. This combined profile is not present in any clinically available compound, and even in the literature has only been demonstrated for its close congener, PPL-101.

Based upon all of these efficacy and initial pharmacokinetic and safety evaluations, Phoenix PharmaLabs is anxious to take PPL-103 through the next steps required to initiate clinical trials. Those next steps correspond to the experiments described in this application. These will include all safety pharmacology required to file an IND and begin clinical trials as an analgesic in humans. The steps required are described in detail below. We currently have a team of experts advising us on the clinical trials required for this type of compound. After the safety toxicology is completed and an IND has been filed, we intend to move quickly into the clinical evaluation of PPL-103 for acute and chronic pain.

As discussed above, there are no other compounds with the *in vitro* and *in vivo* profile of PPL-103. We strongly believe that a compound with this profile, a partial agonist at kappa, mu, and delta receptors, with very low efficacy at mu, will act as a potent analgesic in humans without the normal opiate side effects, including constipation, respiratory depression, and addiction liability.

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Phoenix PharmaLabs, Inc.

Proposed Term Sheet for Series A Preferred Shares of Phoenix PharmaLabs, Inc.

This term sheet (this "Term Sheet") summarizes the principal terms of the Series A Preferred Stock financing (the "Financing") of Phoenix PharmaLabs, Inc., a Utah corporation (the "Company"). This Term Sheet is not intended to, and does not, create any legally binding obligations; and any legally binding obligations between or among the parties will be created only upon the execution and delivery by all parties of definitive agreements. This Term Sheet is not a commitment to invest and is conditioned on the completion of due diligence, legal review and documentation that is satisfactory to the prospective investors and the Company. All dollar amounts are in U.S. Dollars. This Term Sheet shall be governed in all respects by the laws of the State of Delaware (except to the extent that the laws of the State of Utah govern the corporation) without regard to the rules of conflict of laws of such state or any other jurisdiction that would cause the laws of another jurisdiction to apply.

Offering Terms

<i>Securities and Amount Offered:</i>	Minimum of \$10 million (the " <u>Minimum Amount</u> "); Maximum of \$15 million (the " <u>Maximum Amount</u> ") of the Company's Series A Preferred Shares (the " <u>Series A Preferred Shares</u> ").
<i>Price:</i>	\$113.93 per Series A Preferred Share (the " <u>Original Issuance Price</u> ").
<i>Pre-Money/Post-Money Valuation:</i>	The Original Purchase Price is based upon a fully-diluted pre-money valuation of U.S. \$30 million and a fully-diluted post-money valuation of U.S. \$45 million, assuming the Maximum Amount is sold (including an employee pool representing 10% of the fully-diluted post-money capitalization).
<i>Initial Closing Date; Subsequent Closings:</i>	The initial closing to occur as soon as practicable following negotiation and execution of definitive documentation and satisfaction of the conditions to closing (the " <u>Initial Closing</u> " and the date on which the Initial Closing occurs, the " <u>Initial Closing Date</u> ").

If the Maximum Amount is not issued at the Initial Closing, then additional Series A Preferred Shares (not to exceed the Maximum Amount, inclusive of the Series A Preferred Shares issued at the Initial Closing) may be issued and sold at one or more subsequent closings (each, a “Subsequent Closing”) occurring during the 90-day period immediately following the Initial Closing Date, each on the same terms as the Initial Closing, but, in any event, no later than December 15, 2019, unless extended in the sole discretion of the Company.

Capitalization:

Set forth in Exhibit A is the Company’s capital structure before and after the Initial Closing, assuming issuance of the Maximum Amount at the Initial Closing.

Dividends:

The Series A Preferred Shares will participate in any dividends or distributions declared and paid on the Company’s shares of Common Stock (“Common Stock”) on an as-converted into Common Stock basis. The Series A Preferred Shares will carry an annual 3% dividend, which may be paid in kind at the Company’s election, payable upon liquidation.

Liquidation Preference:

In the event of any liquidation, dissolution or winding up of the Company, the proceeds shall be paid as follows:

First, pay one time the Original Issuance Price plus issued and unpaid dividends on each price per share. Thereafter, the Series A Preferred Shares participate with the Common Stock pro-rata on an as-converted basis.

A merger or consolidation (other than one in which shareholders of the Company own a majority by voting power of the outstanding shares of the surviving or acquiring entity) and a sale, lease, transfer, exclusive license or other disposition of all or substantially all of the assets of the Company for all or substantially all indications will be treated as a liquidation event (a “Deemed Liquidation Event”), thereby triggering payment of the liquidation preferences described above, unless the holders of a majority of the Series A Preferred Shares elect otherwise.

Protective Provisions:

So long as 25% of the Series A Preferred Shares are outstanding, in addition to any other vote or approval required under the Company’s Articles of Incorporation, as amended (the “Articles”), the Company will not,

without the written consent of the holders of at least a majority of the Series A Preferred Shares, either directly or by amendment, merger, consolidation, or otherwise:

(i) liquidate, dissolve or windup the affairs of the Company, or effect any specified type of merger or consolidation or any other specified Deemed Liquidation Event; (ii) amend, alter, or repeal any provision of the Articles in a manner that would adversely affect any right, preference, privilege or voting power of the Series A Preferred Shares; (iii) amend or change in any respect the rights, preferences or other terms of the Series Preferred Shares; (iv) create or authorize the creation of or issue any other security convertible into or exercisable for any equity security, having rights, preferences or privileges senior to or on parity with the Series A Preferred Shares, or increase the authorized number of Series A Preferred Shares; or (v) purchase or redeem or pay any dividend on any series or class of the Company's equity securities, including, but not limited to, Common Stock, prior to the Series A Preferred Shares.

Voting Rights:

The Series A Preferred Shares shall vote together with the shares of Common Stock on an as-converted basis, and not as a separate class, except as required by law, subject to the Protective Provisions above.

Optional Conversion:

Each Series A Preferred Share initially converts 1:100 to Common Stock at any time at option of the holder thereof, subject to adjustments for share dividends, splits, combinations and similar events and as described below under "*Anti-dilution Provisions.*"

Mandatory Conversion:

Each Series A Preferred Share will automatically convert into Common Stock at the then applicable conversion rate in the event of (i) (x) the closing of an underwritten public offering, (y) the consummation of a transaction pursuant to which the Company merges with or into a direct or indirect subsidiary of a public company traded on any major exchange or over-the-counter market and subject to the reporting requirements of the Exchange Act or (z) the initiation of trading of the Common Stock on any major stock exchange or over-the-counter market, or (ii) upon the written consent of the holders of at least a majority of the outstanding shares of the Series A Preferred Shares.

Anti-dilution Provisions:

If the Company issues additional shares, or securities convertible into additional shares, at a purchase price, or conversion price, as applicable, that is less than the current Series A Preferred Share conversion price, then the Series A Preferred Share conversion price will be reduced to the price at which the new shares are issued or the per share conversion price of the new convertible securities, as applicable.

The following issuances shall not trigger an anti-dilution adjustment:

(i) securities issuable upon conversion of any of the Series A Preferred Shares, or as a dividend or distribution on the Series A Preferred Shares; (ii) securities issued upon the conversion of any debenture, warrant, option, or other convertible security; (iii) Common Stock issuable upon a share split, share dividend, or any subdivision of shares of Common Stock; (iv) Common Stock (or options to purchase Common Stock) issued or issuable to employees or directors of, or consultants to, the Company pursuant to any plan approved by the Company's Board of Directors; (v) Common Stock issuable in connection with acquisitions by the Company, which are approved by the Company's Board of Directors; or (vi) issuance of securities with respect to which holders of at least a majority of the outstanding Series A Preferred Shares determine shall not trigger anti-dilution adjustment.

Drag Along:

Holders of Series A Preferred and holders of Common Stock will agree to vote their respective shares in favor of a Deemed Liquidation Event or transaction in which 50% or more of the voting power of the Company is transferred and which is approved by the Board of Directors and the holders of greater than 50% of the outstanding Series A Preferred Shares (the "Electing Holders"), so long as the liability of each shareholder in such transaction is several (and not joint) and does not exceed the shareholder's pro rata portion of any claim, and the consideration to be paid to the shareholders in such transaction will be allocated as if the consideration were the proceeds to be distributed to the Company's shareholders in a liquidation under the Articles of Incorporation, as then in effect.

Right of first Refusal/Right of Co-Sale (Take-me-Along):

The Company first and holders of Series A Preferred Shares second (to the extent assigned by the Board of

Directors) will have a right of first refusal with respect to any equity securities of the Company proposed to be transferred by such persons to be agreed upon and under conditions to be defined. Subject to customary exceptions, before any such person may sell Common Stock, he or she will give the holders of Series A Preferred Shares an opportunity to participate in such sale on a basis proportionate to the amount of securities held by the seller and those held by the Series A Preferred Shareholders.

Registration Rights:

Each holder of Series A Preferred Shares will have customary registration rights with respect to all Series A Preferred Shares held by such investor and all Series A Preferred Shares issuable upon conversion of the Series A Preferred Shares held by such investor, as applicable.

Information Rights:

Holders of Series A Preferred Shares will have customary information and inspection rights, including the right to receive annual and quarterly financial statements and business reports of the Company and to have one Series A Preferred Share designee reasonably inspect during normal business hours, once per calendar year, the Company's books and records, and to receive any other information, document or material of the Company reasonably requested by a designee of the holders of Series A Preferred Shares and/or which is provided to any other investors in the Company, subject to standard confidentiality, privilege and work-product provisions and doctrines.

Pre-Emptive Rights:

Each Series A Preferred Share holder of the Company who holds at least 5% of the Company's issued and outstanding Series A Preferred Shares (each, a "Qualified Shareholder") will have preemptive rights to purchase its pro rata share of new securities issued by the Company with a right of over-allotment.

Board Membership:

From the Initial Closing, the Board of Directors of the Company shall consist of 5 members, 1 of whom shall be appointed by the holders of the Series A Preferred Shares.

*Representations, Warranties,
Covenants and Conditions:*

The purchase documents related to this financing and governance of the Company shall have standard representations, warranties, covenants and conditions to

closing, including satisfactory completion of financial and legal due diligence.

Key Person Life Insurance:

The Company shall purchase key person life insurance for the lives of key personnel in an amount to be determined, proceeds to be payable to the Company.

Subscription:

The minimum subscription is \$1,000,000, subject to the Company's discretion to accept smaller amounts.

Use of Proceeds:

The Company intends to use the proceeds of this Financing to fund the advancement of PPL-103 through Phase I safety trials, including the study of side effects as well as sufficient Phase II efficacy studies to establish Proof of Concept in humans for pain, and if sufficient capital remains, for addiction therapy. The trials shall be conducted in the United States or in another country where clinical trials may be conducted following FDA protocols.

Escrow Agent:

[To be determined] (the "Escrow Agent") shall act as escrow agent for the Financing.

Company Counsel

Company counsel to draft documents.

Company's

U.S. Counsel:

Greenberg Traurig, P.A.
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EXHIBIT A

Phoenix Summary Capitalization Table					
Pre-Financing Capitalization as of 8/12/2019					
Class	Shares Authorized	Shares Issued and Outstanding	Common Stock Equivalent	Fully Diluted Shares	Fully diluted ownership
Common Stock	55000000				
Founders and Management		15,174,110	15,174,110		
Angel Shareholders		9,929,536	9,929,536		
Netcapital		1,228,792	1,228,792		
Total Common Stock Issued and Outstanding			26,332,438	26,332,438	100%
Preferred Stock	5,000,000	0	0		
Total Preferred Stock Issued and Outstanding			0	0	0%
Totals			26,332,438	26,332,438	100%
Pro Forma Post-Financing Capitalization: \$15M Investment					
Class	Shares Authorized	Shares Issued and Outstanding	Common Stock Equivalent	Fully Diluted Shares	Fully diluted ownership
Common Stock	55,000,000				
Founders and Management		15,174,110	15,174,110		
Angel Shareholders		9,929,536	9,929,536		
Netcapital		1,228,792	1,228,792		
Total Common Stock Issued and Outstanding			26,332,438	26,332,438	67%
Preferred Stock	5,000,000				
Series A Investors		131,662	13,166,219		
Total Preferred Stock Issued and Outstanding			13,166,219	13,166,219	33%
Totals				39,498,657	100%