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Pre-IND Development of PPL-103: A Potent Opioid Analgesic that is Safe, Non-Addicting, and Free of Other Dangerous Opioid Side Effects

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14. ABSTRACT

Background: Mu opioid receptor agonists are the gold standard for opioid pain relief, however, they exhibit grave side effects, including abuse and addiction liability, constipation, respiratory depression, and death from overdose. Kappa agonists are dysphoric and thus not clinically useful. Phoenix is developing PPL-103: a kappa and mu partial agonist with potent analgesic activity and little to no abuse liability, constipation or respiratory depression. PPL-103 is efficacious in several acute and chronic pain models, is not self-administered in rats but is clearly not dysphoric like other kappa agonists, as determined by a conditioned place preference assay. PPL-103 substitutes for morphine and blocks morphine withdrawal, suggesting that it could be given to morphine-naive or morphine-dependent patients without inducing withdrawal.

Objective: Through this project we propose to advance PPL-103 for safe, potent, non-addicting pain relief by validating the analgesic activity and non-addicting nature in non-human primates, producing of GLP material, completing the necessary package of pre-clinical testing and filing an IND with the FDA, to fully preparing for initiation of first-in-man clinical trials.

Specific aim #1: GLP scale-up and manufacturing of PPL-103
Specific aim #2: Complete preclinical efficacy studies in non-human primates.
Specific aim #3: Complete preclinical in vitro and in vivo GLP studies of PPL-103
Specific Aim #4: Filing an IND and preparation for Phase I human clinical trials.

Study Design: In Aim 1, we will optimize and scale up the manufacture of PPL-103 to produce sufficient GLP grade material to support Aims 2 and 3. In Aim 2 we will validate PPL-103 as being potent, safe, and non-addicting in non-human primate models. In Aim 3 perform genetic toxicology, safety pharmacology, general toxicology, reproductive and developmental toxicology, pharmacokinetics. We shall then produce and file an IND with the FDA and develop a clinical trial plan for first-in-man clinical trials of PPL-103.

Relevance: Based on the data that we have so far, it appears that PPL-103 can be a "game changer" for pain management and will reduce costs of medical services logistics. It has very promising potential to become a superior centrally-acting analgesic for treatment of acute post-surgical pain, as well as acute and chronic pain during rehabilitation. It could be particularly well suited for treatment of chronic pain during extended rehabilitation due to the fact that it appears to have little or no potential for abuse and addiction, as well as substantially reduced risk of death from overdose and the lack of constipation side effects.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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INTRODUCTION

The purpose of this grant is the preclinical development of PPL-103. PPL-103 is an opioid analgesic that partially activates all three opioid receptors, with highest efficacy at kappa receptors and lowest efficacy at mu receptors. This combination of activities produces potent analgesia but neither euphoria nor dysphoria. Therefore, this compound is not self-administered in rats and has lower abuse potential. In this grant we will continue translational studies to determine analgesic activity and abuse liability in non-human primates. We will also synthesize a sufficient amount of GLP (Good Laboratory Practices) grade of PPL-103 to conduct preclinical safety studies prior to submission of an IND.

KEYWORDS

Non-addicting analgesic, PPL-103, non-human primate, preclinical safety studies, GLP synthesis.

ACCOMPLISHMENTS

The major goals are listed below:

	Timeline
Major Task 1. GLP scale-up and manufacturing of PPL-103	Months
Subtask 1. Pilot GLP manufacturing and process optimization	1-9
Subtask 2. Develop and validate quality control assays	9-12
Subtask 3. Scale-up and GLP manufacturing	9-15
Subtask 4. Test PPL-103 product for stability	9-27
Subtask 5. Formulation and Drug Product Development.	15-21
Milestone(s) Achieved	3
Major Task 2. Complete preclinical efficacy studies in non-human primates.	
Subtask 1. Obtain IACUC approvals	1
Subtask 2. Obtain ACURO approval	1-2
Subtask 3. Determine potency for reducing acute thermal and inflammatory pain	2-4
Subtask 4. Abuse liability will be studied in a model of self-administration	4-7
Subtask 5. Physical dependence/withdrawal signs following repeated PPL-103 administration measured by the telemetry device.	7-10
Subtask 6. Acute effects of PPL-103 will be evaluated in freely moving monkeys	10-12
Milestone(s) Achieved:	5
Major Task 3. Complete preclinical in vitro and in vivo GLP studies of PPL-103	
Subtask 1. Obtain IACUC approvals	10
Subtask 2. Obtain ACURO approval	11
Subtask 3. Genetic toxicology	12-15
Subtask 4. Safety pharmacology	12-18
Subtask 5. General toxicology	15-24
Subtask 6. Pharmacokinetics	15-21
Milestone(s) Achieved:	1
Major Task 4. **Filing an IND and preparation for Phase I human clinical trials.**	
Subtask 1. Pre-IND meeting	9-12
Subtask 2. IND preparation and filing	25-27

Major Task 1 (Scale-up of PPL-103), subtasks 1 and 2 are completed, and scale-up is underway. As described in our previous reports, the analgesic PPL-103 is a 3-OH-levo-morphinan molecule with a chiral N-substituent. The synthesis of PPL-103 requires the large-scale preparation of this morphinan, followed by introduction of the N-substituent. Since two diastereomers of the N-substituted morphinan could result from the attachment of the chiral N-substituent, final separation of the diastereomers completes the preparation of PPL-103. We currently have received a 185 g batch at 99% purity, some of which was sent to Wake Forest University for NHP studies. Dalton Pharma Services is now working on a 2 kg batch, under GLP conditions, that will be sufficient for all of the preclinical studies.

Major Task 2 (non-human primate studies), subtasks 1-4 and 6 have been completed at Wake Forest University.

As seen in **Figure 1**, PPL-103 has very potent antinociceptive activity in the rhesus monkey. As expected for a kappa agonist, there is relatively mild sedation at analgesic doses. **Table 1** shows the sedation rating scale.

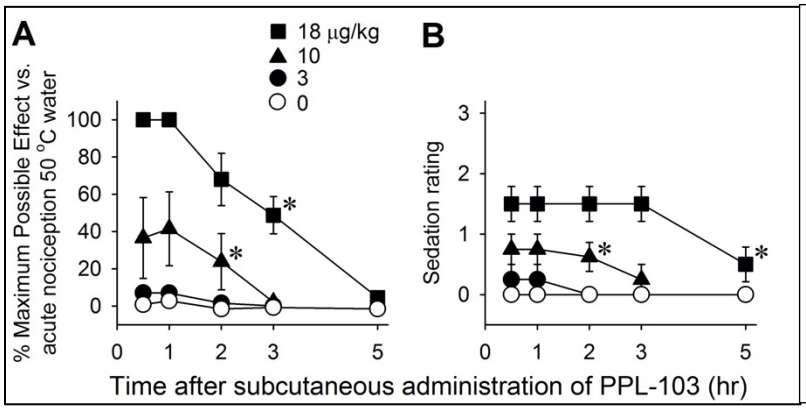

Figure 1. A. Antinociceptive effects of systemic PPL-103 in the warm water tail flick test in rhesus monkeys (n=4). **B. Sedation rating at analgesic doses.** * p<0.05 vs. vehicle from 0.5 hr to the corresponding time point

Figure 2 compares the potency of PPL-103 and morphine in the warm water tail withdrawal assay. As can be seen, PPL-103, with an ED_{50} of 6 µg/kg, is approximately 100 times more potent than morphine in this assay.

Modified sedation rating scale

Grade	Sedation
0	No observable sedation; monkey is alert to environment
1	Monkey is attentive to ordinary movements of observer
2	Monkey responds to clapping noise in room
3	Monkey responds only to noises generated by knocking on its chair
4	Monkey responds only to clapping noise ~2 feet away from its head
5	Monkey responds only to touch
6	Monkey does not respond to touch

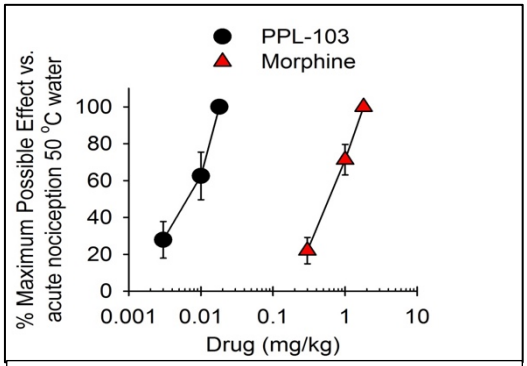

Figure 2. Comparison of antinociceptive potency of PPL-103 versus morphine. PPL-103 ED50: 0.006 mg/kg, 95% CI: 0.003-0.016 mg/kg. Morphine ED50: 0.64 mg/kg

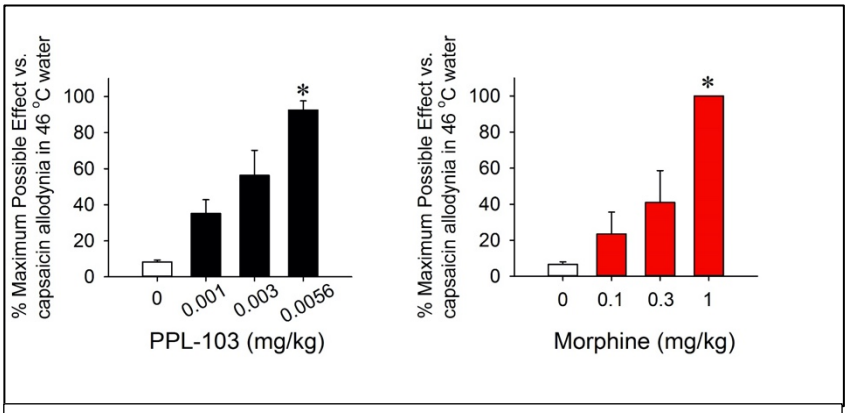

Figure 3. Inhibitory effects of systemic PPL-103 on capsaicin-induced allodynia in rhesus monkeys (n=4). * p<0.05 vs. vehicle 3 out of 4 NHPs showed sedation after given 0.0056 mg/kg of PPL-103.

As seen in **Figure 3**, PPL-103 is also very potent in blocking inflammatory pain, with an ED_{50} of approximately 3 µg/kg, and once again is 100 times more potent than morphine. In this experiment, there was some sedation at the highest dose tested.

Abuse liability studies have also been carried out in NHPs. As seen in **Figure 4**, at each dose, PPL-103 shows a slight and non-significant increase in drug injections when using a progressive ratio schedule of reinforcement. This is in comparison to oxycodone, which is

significantly self-administered. These results suggest that PPL-103 might have a very mold reinforcing effect, but is very different than normal mu opiates, and is unlikely to be abused in people.

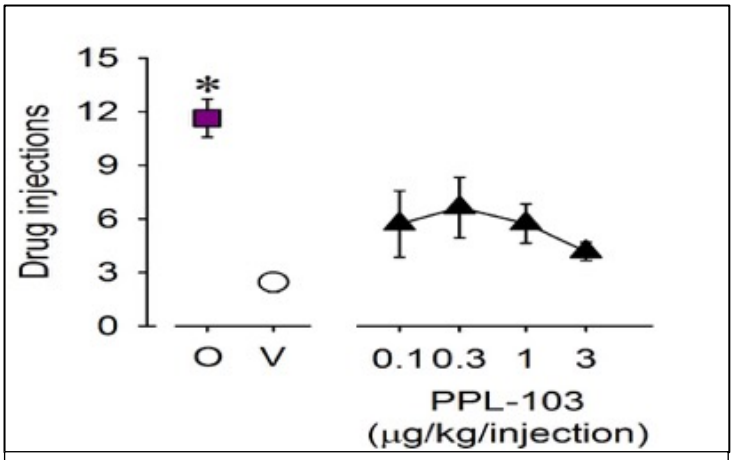

Figure 4. Self-administration of PPL-103 in rhesus monkeys (n=4). Note: O: Oxycodone, 3 ug/kg/inj; V: vehicle * p < 0.05 for oxycodone vs. vehicle

Respiratory and cardiovascular effects were also conducted in the rhesus monkeys after administration of PPL-103. As seen in **Figure 5A,** PPL-103 induces a decrease in respiration, both respiratory rate and minute volume. This is a somewhat surprising result, based upon the rodent studies. However, it is clear that the respiratory depression is not dose dependent, with all three doses producing equivalent depression. This suggests a ceiling effect, probably because of the partial agonist activity. This result is consistent with the rodent data, which demonstrated that lethality did not occur until 300 times the effective analgesic dose. We would like to conduct studies to determine if the respiratory depressant effects are mediated by mu or kappa receptors.

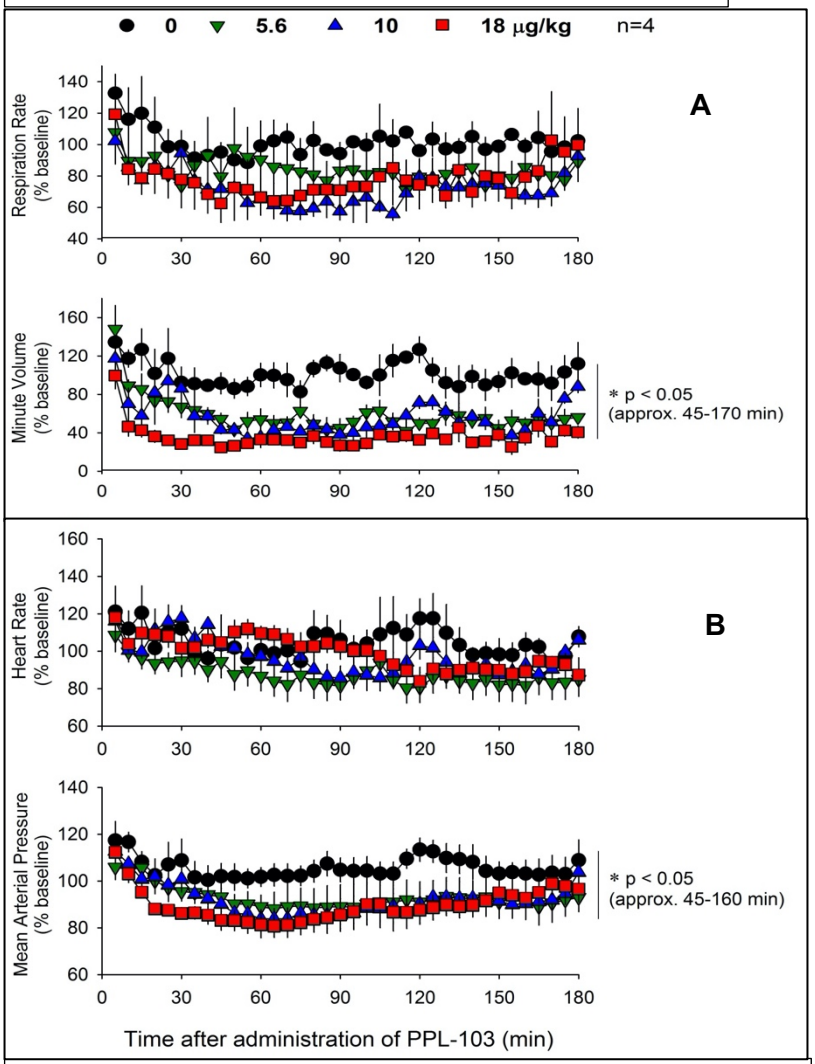

Figure 5. (A) Respiratory and (B) cardiovascular effects of PPL-103 in rhesus monkeys.

PPL-103 also caused slight hypotensive effects at analgesic doses (**Figure 5B**). Once again, these effects were not dose dependent, with similar effects at each dose tested, suggesting some sort of ceiling effect. These results suggest that we should carefully examine the respiratory and cardiovascular effects of PPL-103 in our first in human Phase I clinical trials.

Major task 3 is underway. Our CRO that will conduct the preclinical in vitro and in vivo evaluations (ITR Canada) has completed Subtask 1 (IACUC approval) and Subtask 2 (ACURO approval) is finally nearing completion. We have responded to ACURO's comments to the protocols, and we expect approval soon. The timing for this is appropriate, as the large quantity of GLP material should soon be available from Dalton. We hope to have the preclinical package finished in the next 10 months to keep on schedule for this program.

IMPACT

As discussed above, the program for this translational project is on track. The NHP studies are almost complete and preclinical safety evaluations will begin soon. The results have generally been positive and we have high hopes that PPL-103 will eventually have a significant impact on treatment of acute and chronic pain.

CHANGES/PROBLEMS.

We have no changes and no problems to report in the successful accomplishment of the proposed tasks.

PRODUCTS

The product of 2 kg GLP grade PPL-103 should be completed very soon. 185 g of research grade material are available and have been used for the non-GLP studies that have already been conducted.

Name: *Lawrence Toll*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): LRTOLL
Nearest person month worked: *2.4*
Contribution to Project: *Dr. Toll has directed the overall project. As such, he has participated in discussions with subcontractors Dalton Pharma Services and ITR with respect to synthesis of PPL-103 and coordinated with Wake Forest University and ITR for ACURO approval .*

Name: *John Lawson*
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Contribution to Project: *Dr. Lawson has expertise in synthesis of PPL-103, and as such has directed the synthetic scheme being developed by Dalton Pharma Services.*

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Researcher Identifier (e.g. ORCID ID): WCROSSMANSO
Nearest person month worked: *3.6*
Contribution to Project: *Mr. Crossman has managed project execution including contract administration and optimization of communications, coordination and integration between the various project contributors.*

Name: *Daniel Levy*
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Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *2.0*
Contribution to Project: *Dr. Levy is an expert in synthetic and process chemistry and scale-up. He has been involved in all discussions with Dalton Pharma Services to insure appropriate scale-up and manufacturing of PPL-103.*

Name: *Mei-Chuan (Holden) Ko*
Project Role: *Consortium PI*
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Contribution to Project: *Dr. Ko is an expert in translational research using non-human primates, primarily to study pain and drug abuse. He has directed the studies using rhesus monkeys described in this Annual Report*

Name: *Huiping Ding*
Project Role: *Pharmacologist*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *4.8*
Contribution to Project: *Dr. Ding is an expert in non-human primate studies on pain and performed a large number of the experiments at Wake Forest University.*

Name: *Kelsey Reynolds*
Project Role: *Technician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *3.6*
Contribution to Project: *Ms Reynolds assisted with the non-human primate studies at Wake Forest University*

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SPECIAL REPORTING REQUIREMENTS

None

APPENDICES

None