

ROFLEX™: A NOVEL FORMULATION FOR TREATMENT OF RESPIRATORY AND ANXIETY DISORDERS

Pondera Biotechnologies, Inc.

CLINICAL NEEDS:

Respiratory Disorders:

Respiratory disorders, including asthma and COPD, are very serious life-threatening medical conditions, which currently impact 8.8% of the U.S. population, according to the Behavioral Risk Factor Surveillance System (BRSS).¹ There has been a long-standing use of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) inhibitors (e.g., theophylline) for the treatment of respiratory conditions² including the recent FDA approval and marketing of a more potent selective cAMP-PDE4 inhibitor, roflumilast, for COPD by Forest Labs (Daliresp®).³ While effective for these respiratory disorders, these cAMP-PDE inhibitors are well-known for their neuropsychiatric side effects, including anxiety, depression, insomnia, suicidal impulses, and other symptoms of emotional and physical distress.²

Clinical studies during the roflumilast drug development program found that “psychiatric symptoms such as anxiety, depression, and insomnia were two to three times as common in the roflumilast groups as in the placebo groups. There were two cases of attempted suicide and three cases of completed suicide in the roflumilast groups and none in the placebo groups.”⁴

Moreover, since then, there have been an unusual number of adverse psychiatric events (APE) for roflumilast, including serious suicidal ideation.⁵ According to Forest Labs’ Daliresp® home page, the first risk information provided is: “**DALIRESP may cause mental health problems, including suicidal thoughts and behavior.** Some people taking DALIRESP may develop mood or behavior problems including thoughts of suicide or dying, attempt to commit suicide, trouble sleeping (insomnia), new or worse anxiety, new or worse depression, acting on dangerous impulses, or other unusual changes in behavior or mood.”⁶ [Bold-faced type original].

Therefore, there is a clear clinical need to develop a method to reduce these undesirable neuropsychiatric side effects of cAMP-PDE inhibitors for patient safety, mental health, and compliance.

Moreover, there is a well known pathophysiologic vicious cycle between *respiratory* distress, such as dyspnea, and *emotional* distress, such as anxiety and depression.⁷ Respiratory distress typically triggers anxiety and panic, while at the same time, anxiety and depression tend to exacerbate respiratory conditions. In fact, clinical research suggests that up to one-third of patients with asthma concurrently suffer from an anxiety disorder.⁸ Similarly, anxiety and depression have a much higher prevalence in COPD than other advanced medical problems.⁹ Therefore, the neuropsychiatric side effects of cAMP-PDE inhibitors unfortunately tend to exacerbate the predisposition of respiratory patients toward anxiety and depressive disorders. Furthermore, by increasing anxiety and depressive symptoms, cAMP-PDE inhibitors may have an iatrogenic effect, which *limits* and *masks* their true potential for relief of respiratory conditions.

As Maurer et al (2008) argue, “studies evaluating treatment approaches for depression and anxiety in COPD are a priority; such studies should address the effectiveness of different types of pharmacologic treatment.”⁹ Clearly, a method that would not only *reduce* the neuropsychiatric side effects of cAMP-PDE inhibitors, but also literally *reverse* them to produce anxiolytic benefits, would provide a new generation treatment for respiratory disorders, which is currently not available in clinical practice. ROFLEX™ can provide a new level of *relief from both respiratory and emotional distress* for millions of patients with serious respiratory disorders, and dramatically improve patient physical and mental health, compliance, and overall well-being.

Anxiety Disorders:

There is a serious need for a safe and effective pharmaceutical treatment for chronic anxiety. According to the National Institute of Mental Health, 28.8% of the adult U.S. population will suffer from an anxiety disorder.¹⁰ Specific anxiolytic medications, including the popular benzodiazepines, while often effective for acute anxiety, are well known for noxious side effects including sedation, memory and other cognitive impairments, hyperexcitability, tolerance, withdrawal symptoms and dependence, and are not clinically appropriate for chronic anxiety or long-term use.¹¹ Non-specific, longer-term pharmaceuticals, including anti-depressant medications (e.g., SRRIs) have some clinical benefits for anxiety, but appear to be inconsistent and, at times, anxiogenic with other side effects including sexual dysfunction, sleepiness, and weight gain.¹² Finally, while

psychotherapy, especially cognitive behavioral therapy (CBT), has been shown to reduce anxiety symptoms,¹³ it is often insufficient to resolve more serious anxiety disorders and requires specialized services not accessible or attractive to many people. Therefore, there is a clear clinical need for ROFLEX™ *ULTRA*, a safe and effective anxiolytic medication for the relief of suffering for millions of anxiety patients, which targets the underlying neuro-biochemical imbalances responsible for emotional and physical distress.

NOVEL PHARMACEUTICAL FORMULATIONS:

There is significant preclinical¹⁴ and clinical¹⁵ evidence to support the benefit of adding ultra-low-dose naltrexone (ULDN) to cAMP-PDE inhibitors for the safe and effective long-term treatment of *both* respiratory and anxiety disorders. This cotreatment pharmaceutical formulation is based on decades of published scientific research^{14,15} and is the basis for two recently issued patents for respiratory disorders¹⁶ and anxiety disorders¹⁷ that have been assigned to Pondera Biotechnologies, Inc. This novel method simultaneously reduces the neuropsychiatric side effects of cAMP-PDE inhibitors, such as roflumilast, ibudilast, and theophylline, for the treatment of respiratory disorders and enhances their therapeutic benefits by reducing emotional and physical distress, which frequently exacerbates symptoms and severity of respiratory disorders.¹⁶ In addition, this method can be used to directly reduce emotional and physical distress for individuals suffering from a variety of neuropsychiatric and neurodevelopmental conditions, including chronic anxiety disorders.¹⁷ Evidence suggests that selective cAMP-PDE4 inhibitors (e.g., roflumilast) are particularly potent agents for this cotreatment formulation.¹⁴⁻¹⁸ The net effect of this novel pharmaceutical is to *unmask* the true capacity of cAMP-PDE inhibitors for the *safe and effective treatment of both respiratory and emotional distress disorders*.

SCIENTIFIC AND PRECLINICAL EVIDENCE:

There is significant scientific evidence that the neuropsychiatric side effects produced by cAMP-PDE inhibitors (e.g., roflumilast, rolipram, theophylline, caffeine) are caused by their stimulation of the release of endogenous opioids (i.e., endorphins), mediated by their marked elevation of cAMP.^{14,18} This stimulated release of *endogenous* opioids triggers prolonged excessive *excitatory* opioid receptor signaling, which produces long-lasting emotional and physical distress, including anxiety, agitation, insomnia, despair, and

hyperalgesia, similar to the noxious side effects of *exogenous* opioids (e.g., morphine, oxycodone).^{14,18}

Based on three decades of published preclinical research, Drs. Crain and Shen discovered a simple method to switch opioid receptors from excessive *excitatory* signaling to normal *inhibitory* signaling¹⁹, which converts distress and hyperalgesia to calm and comfort when the receptors bind with either *exogenous* or *endogenous* opioids.^{14,18-20} By adding an *ultra-low-dose* of an opioid *antagonist* (e.g., naltrexone or naloxone) to an *exogenous* opioid *agonist* (e.g., morphine or oxycodone), typical opioid side effects were significantly reduced and even reversed in both preclinical^{19,20} and large-scale clinical trials²¹. While other opioid receptor “switching” agents have been discovered (e.g., agents that increase sulfates, such as n-acetyl cysteine (NAC) and magnesium sulfate¹⁴), *ultra-low-dose naltrexone* (ULDN) was the most specific, potent, and effective oral “*opioid receptor switcher*” found in these studies¹⁴.

More recent studies have applied these discoveries regarding the *bimodal nature of opioid receptors* to cAMP-PDE inhibitors.^{14,18} By systematically combining a cAMP-PDE inhibitor (e.g., rolipram, theophylline) with ULDN in an acute stress paradigm with rodents, the typical signs of long-lasting emotional and physical distress produced by the cAMP-PDE inhibitors alone were eliminated.¹⁸ In fact, these noxious symptoms were *converted* to a *prolonged* state of calm, reduced reactivity to stress, and increased pain tolerance.¹⁷ Moreover, given the potency of a selective cAMP-PDE4 inhibitor, *ultra-low-doses* of rolipram, combined with ULDN, produced remarkably long-lasting distress relieving effects.¹⁸

Systematic studies have confirmed that these processes are mediated through the endogenous opioid system.^{14,18-20} Specifically, by elevating cAMP levels, cAMP-PDE inhibitors stimulate the release of endogenous opioids (i.e., endorphins) that trigger excessive *excitatory* (distress-producing) signaling, which is rapidly *converted* to *inhibitory* (distress-relieving) signaling when ULDN is added.^{13,17} Not only did this line of preclinical research reveal a simple method to reduce the neuropsychiatric side effects of cAMP-PDE inhibitors, but it also led to a novel anxiolytic formulation, combining an *Endorphin Enhancer* (e.g., cAMP-PDE inhibitor) with an *Opioid Receptor Switcher* (e.g., ULDN), which *unmasks* the remarkable *distress-relieving* power of endorphins.^{13,14} These studies found that selective cAMP-PDE4 inhibitors (e.g., rolipram) were particularly potent Endorphin Enhancers.¹⁸

PRELIMINARY CLINICAL VALIDATION STUDIES

This preclinical research inspired the design of a series of preliminary clinical studies with over 120 participants using a variety of Endorphin Enhancers (e.g., cAMP-PDE inhibitors) and Opioid Receptor Switchers (e.g., ULDN, NAC).¹⁵⁻¹⁷ In addition to non-specific cAMP-PDE inhibitors (e.g., theophylline, caffeine), the selective cAMP-PDE4 inhibitor, roflumilast, was used.¹⁶⁻¹⁷ Throughout these studies, participants typically experienced at least some degree of emotional and/or physical distress, including anxiety, restlessness, malaise, and hyperalgesia, when taking a cAMP-PDE inhibitor alone.¹⁵⁻¹⁷ However, when an Opioid Receptor Switcher, such as ULDN or NAC, was added, these side effects were generally eliminated and, more remarkably, most participants experienced a significant sense of calm, comfort, well-being as well as enhanced mental clarity and energy.

Induced pain tasks, including a “cold pressor” paradigm, were used to assess participants’ physical and emotional reactions to acute stress. When administered alone, cAMP-PDE inhibitors, such as roflumilast and theophylline, generally produced hyperalgesia reflected in reduced pain tolerance and increased emotional distress. However, when combined with ULDN or NAC, participants experienced a remarkable reduction in both physical and emotional distress, with increased pain tolerance to the level of low-dose opioid pain medications, yet with none of the noxious side effects typically experienced with these drugs. While the endorphinergic formulation provided pain relief, the most dramatic benefit was the reduced emotional distress typically experienced during these stressful pain induction paradigms, especially for those with underlying neuropsychiatric conditions, such as chronic anxiety. These clinical findings were similar to those shown in earlier preclinical studies¹⁸ and demonstrate the distress relieving potency of *endogenous* opioids comparable to *exogenous* opioids.

Exploratory case studies of 26 patients suffering from chronic anxiety and depression showed a marked reduction in anxiety, obsessions and compulsions, irritability and anger, aches and pains, and cravings for alcohol, drugs, and food with daily administration of one of these pharmaceutical cotreatment formulations for a period of 2 to 10 months.^{16,17} The most effective formulation in these case studies was ultra-low-dose roflumilast with ULDN (both about 0.002% of conventional dose), demonstrating the important clinical potential of ROFLEX™ ULTRA.

Long-term clinical case studies with more than 200 patients with a variety of neuropsychiatric distress-related conditions, including chronic anxiety and depression, were treated over a two-year period with a nutraceutical formulation combining an Endorphin Enhancer (e.g., caffeine) with an Opioid Receptor Switcher (e.g., NAC).¹⁵ Findings demonstrated relief of emotional and physical distress, including reduced anxiety, depression, anger, and cravings as well as increased calm, comfort, and positive mood, for most patients.¹⁵ Given the much greater potency of selective cAMP-PDE4 inhibitors observed in preclinical and preliminary clinical case studies, longer term clinical case studies are underway with ROFLEX™ *ULTRA*, which are demonstrating even more effective anxiolytic and other psychiatric benefits including enhanced mood and relief from cravings.

Cotreatment formulations of conventional-dose roflumilast or theophylline with ULDN were used effectively in case studies of six asthma patients, with clear respiratory and emotional distress-relieving benefits over the course of a year-long trial.¹⁶ Not only were the neuropsychiatric side effects of roflumilast and theophylline eliminated, but the patients experienced remarkable anxiolytic and mood enhancing benefits in addition to effective control of their asthma.¹⁶ Patients were much more able to handle stress in their lives, without experiencing asthma and/or anxiety attacks than ever before. These preliminary case studies demonstrate the safety and effectiveness of regular strength ROFLEX™ in the treatment of respiratory disorders.

Therefore, these preliminary clinical studies confirm that the pharmaceutical combination of roflumilast (and other cAMP-PDE inhibitors) with ULDN has important potential for the treatment of *both* anxiety and respiratory disorders. This discovery reveals an extremely simple method to *unmask* the *respiratory and emotional distress relieving potency of cAMP-PDE inhibitors*, particularly cAMP-PDE4 inhibitors.

PROPOSED DRUG DEVELOPMENT PLAN:

Since the FDA has approved roflumilast for the treatment of COPD, it appears reasonable to focus the initial stage of this drug development program upon the clinical safety and efficacy of adding an ultra-low-dose of naltrexone (ULDN) to a therapeutic dose of roflumilast for the treatment of COPD (ROFLEX™). Clinical trials using roflumilast alone could be used as comparison studies with this cotreatment formulation. If clinical trials are

successful and FDA approval is granted, physicians would also be free to use this formulation, using clinical judgment, for asthma, which is also covered by the same patent. If ROFLEX™ proved successful in the treatment of asthma, additional clinical trials for this condition might well be appropriate. Moreover, a significantly improved pharmaceutical for respiratory disorders is expected to dramatically increase physician and patient acceptance and compliance.

During this initial drug development program, clinical evidence can be obtained regarding the anxiolytic benefits of the cotreatment formulation. If, as predicted, there are clinically meaningful neuropsychiatric benefits from this novel pharmaceutical, the drug development program could enter the next phase. This could include the use of the pharmaceutical for anxiety and other neuropsychiatric symptoms, should physicians determine this application to be appropriate. However, given findings from preclinical and clinical studies, *ultra-low-doses* of *both* roflumilast and naltrexone (ROFLEX™ *ULTRA*) should also be tested for the treatment of anxiety and related neuropsychiatric disorders. If FDA trials are successful, a safe and effective *next generation* pharmaceutical for both acute and chronic anxiety as well as other neuropsychiatric conditions has enormous clinical potential, given their high prevalence and unmet clinical need.

It should be noted that while there is a rationale for starting this drug development program with ULDN combined with roflumilast since it is an FDA-approved and potent selective cAMP-PDE4 inhibitor, the scientific and clinical evidence indicates that other cAMP-PDE inhibitors (e.g., theophylline, ibudilast), combined with ULDN, could also be safe and effective treatments for these indications. These cotreatment formulations are also covered by the approved and pending patents assigned to Pondera Biotechnologies, Inc., which can both support drug development programs as well as prevent competing claims by others using these scientific discoveries and inventions.

PARTNERSHIP AND LICENSING AGREEMENTS:

Pondera Biotechnologies, Inc. is seeking partnership and/or licensing agreements with appropriate pharmaceutical companies for the purpose of funding and conducting this proposed drug development program. Pondera is the sole owner of these patents and has no obligation to, or contracts with, any third parties with regard to these patents.

¹ American Lung Association, Epidemiology and Statistics Unit, “*Estimated prevalence and incidence of lung disease*,” April 2013: <http://www.lung.org/finding-cures/our-research/trend-reports/estimated-prevalence.pdf>

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⁶ www.dailiresphcp.com

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¹⁵ S. Crain, M. A. Crain and S. M. Crain, “Emotional and physical distress relief using a novel endorphinergic formulation,” *Journal of Behavioral and Brain Science*, Vol. 3, No. 6, 2013, pp. 441-453.

¹⁶ S. Crain, W. Crain, S. M. Crain and M. Crain, U.S. Patent No. 8617577 “A method to safely and effectively treat asthma or chronic obstructive pulmonary disease and enhancing safety and efficacy of specific medications.” (Assignee: Pondera Biotechnologies, Inc.)

¹⁷ S. Crain, W. Crain, S. M. Crain and M. Crain, U.S. Patent No 8,741,319 “A method to safely and effectively treat anxiety conditions, symptoms and/or disorders and enhancing safety and efficacy of specific medications.” (Assignee: Pondera Biotechnologies, Inc.)

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