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***Roflex™***

**FOR THE TREATMENT OF CO-MORBID RESPIRATORY**

 **AND NEUROPSYCHIATRIC DISORDERS**

1. ***THE PROBLEM***

Pondera Pharmaceuticals has found the solution to a very serious problem for respiratory patients – *co-morbid* neuropsychiatric disorders, particularly *anxiety*. An estimated 25%1 of the more than 24 million2 COPD patients and 34% of the more than 30 million asthma patients3 in the U.S have anxiety disorders and related neuropsychiatric conditions. The co-morbidity of respiratory and anxiety disorders has been well known for decades, but there has been no safe and effective way to resolve this very serious problem, which has a devastating impact on the patient’s medical condition and needs as well as the healthcare system more generally3,4.

Respiratory patients experience profound worries and panic regarding their health and their very ability to breathe and stay alive, considerably more than most other chronic medical conditions5. As a result, their anxieties, manifested most often in physical distress, including tightness in breathing, leads both to a marked exacerbation of their respiratory condition, including increased inflammation6, as well as heightened fear of their imminent demise. This vicious cycle leads to a dramatic escalation in their urgent use of medical services, including emergency department (ED) visits and frequent as well as prolonged hospitalizations7,8.

Each respiratory flare-up and exacerbation increases anxiety and depression, which creates a vicious cycle of escalating respiratory symptoms as well demand for expensive medical services9.  In a recent COPD-specific study of 7522 managed care patients by GlaxoSmithKline, the annual increased cost of medical care for COPD patients with co-morbid anxiety and depression as compared to COPD patients with the *same* respiratory severity, yet without co-morbidity, was $6,449/patient1. Moreover, an exhaustive 2008 meta-analysis of U.S. insurance claims data for more than 9 million people revealed a disproportionate *increase* in per patient medical costs (*excluding* cost of mental health treatment) associated with co-morbid anxiety of more than 100% for COPD and more than 165% for asthma7, as depicted in the figure below:



By more than doubling per patient healthcare costs due to the increased use of expensive ED visits and prolonged hospitalizations for respiratory exacerbations, co-morbid anxiety and depression in respiratory patients cost the U.S. healthcare system tens of billions of dollars annually.

It is important to note that the co-morbid patients in these studies were already in *both* neuropsychiatric and respiratory treatment. Clearly, current treatment for anxiety and depression is insufficient for respiratory patients for several important reasons:

1. Current anxiety medications (e.g., benzodiazepines) have serious side effects, including sedation, memory, and other cognitive and psychomotor impairments, tolerance and addiction, as well as paradoxical anxiogenic reactions, all of which are more problematic for the elderly10. As a result, they are only indicated for short-term use, though this is often violated, which can lead to long-term medical and emotional problems11.

2. Current depression medications (e.g., SSRI, SNRI) also have serious side effects, including sexual dysfunction, sedation, weight gain, cognitive impairments, as well as paradoxical anxiogenic and depressive reactions, and increased suicide risk, all of which lead to marked compliance problems11.

3. Moreover, clinical studies show that these neuropsychiatric medications are not particularly effective even when taken reliably, with estimates of 10-20% benefits over placebo. As a result many serious questions have been raised about the unacceptable risk-benefit ratio for current anxiety and depressive medications.12

4. Finally, many respiratory patients are resistant to taking additional medications, beyond their required respiratory drugs, especially psychiatric drugs, since they feel that they are being told that their symptoms are “in their head” when they know they have a serious medical problem13. Non-compliance reflects their response that “I’m not crazy, doc!”

Therefore, limited effectiveness and compliance, together with serious side effects of current psychiatric treatment for co-morbid respiratory patients indicate a clear need for a completely new approach to treating this very serious problem. Rather than rely on old psychiatric medications, based on science from decades ago, taken in addition to respiratory medications, Pondera scientists have used groundbreaking discoveries in neuroscience to develop a new treatment method to *simultaneously* treat *both* distress conditions in one *respiratory* medication.

Until now, there has been no solution to this co-morbidity problem, impacting the lives of an estimated 16-20 million COPD and asthma patients in the U.S. alone. In fact, ironically, most current respiratory medications, (e.g. corticosteroids13, cAMP-PDE inhibitors14, and beta 2-agonists15) are well known for *iatrogenically increasing* patients’ neuropsychiatric symptoms. For instance, the one medication that is available to prevent the most serious COPD exacerbations, Daliresp® (roflumilast) has a “black box” warning that it can *increase* the risk of anxiety, depression, and suicide16. Therefore, the patients most at risk for serious respiratory exacerbations are being given medications that *increase* their anxieties and suffering, and therefore, their desperate use of medical services.

1. ***OUR SOLUTION***

Pondera has found the solution to this very serious medical, emotional, and economic problem. Our neuroscientists have devoted the past three decades to researching the endogenous opioid system and cAMP-PDE inhibitors and have discovered a safe and effective method to reduce the emotional and physical distress signals of the brain. Moreover, we have translated this groundbreaking research into a very simple method to dramatically enhance the safety and effectiveness of cAMP-PDE inhibitors for respiratory disorders by adding an ultra-low-dose of naltrexone, an opioid receptor antagonist. This co-treatment formulation not only eliminates the neuropsychiatric side effects of cAMP-PDE inhibitors, but it also transforms them into a powerful *anxiolytic* medication.

A specific cAMP-PDE4 inhibitor, roflumilast, has been shown in a large number of clinical studies to be a potent medication to reduce the risk of respiratory flare-ups and exacerbations in both COPD and asthma patients17. Roflumilast has been approved for COPD treatment and is marketed in the U.S. as Daliresp® and in the E.U. as Daxas®. Our neuroscientists have serendipitously been studying cAMP-PDE4 inhibitors, such as roflumilast, for their marked enhancement of the release of endorphins. The intersection of these independent lines of research led directly to our development of formulations, using cAMP-PDE4 inhibitors, such as roflumilast, for *potent relief of both respiratory and emotional distress.*

Our lead respiratory medication, Roflex™, a patented combination of roflumilast and ultra-low-dose naltrexone (U.S. Patents No. 8,617,57718 and No. 8,741,31919), can be given to *all* COPD and asthma sufferers in order to *simultaneously:* (1) reduce the risk of serious COPD and asthma exacerbations and flare-ups, (2) relieve their anxiety as well as their overall emotional and physical distress, and (3) reduce and/or eliminate the neuropsychiatric side effects of conventional roflumilast (Daliresp®). As a result, they will finally be able to live more comfortably, with dramatically less *actual* respiratory exacerbations than current medications, including roflumilast alone, as well as markedly reduced anxieties and *fears* of having a flare-up and dying.

We expect that the *synergistic* combination of the potent Roflex™ *anti-inflammatory* and *anxiolytic* benefits will dramatically reduce respiratory flare-ups and exacerbations as well as the desperate use of expensive ED visits and prolonged hospitalizations. By decreasing the serious problem of co-morbid anxiety and depression, the reduction in medical, emotional, and economic costs for respiratory patients and the medical community will be remarkable.

Many co-morbid respiratory patients are simply missed by primary care physicians and pulmonary specialists, and others are often reluctant to take psychiatric medications because of their stigma and side-effects1,7,8. Furthermore, given the life-threatening nature of respiratory distress, nearly all COPD and asthma patients experience at least some degree of *emotional* distress, which exacerbates their *respiratory* distress5,6. Since Roflex™ is being developed as the first in-kind *respiratory* medication that simultaneously reduces both *respiratory* and *emotional* distress, thereby preventing respiratory flare-ups and improving patients’ quality of life more than current medications, daily use of Roflex™ could become the standard of care for *all* moderate-to-severe COPD and asthma patients.

Importantly, we expect that the managed care industry would welcome daily use of Roflex™ into the standard of care for moderate-to-severe COPD and asthma, since: (1) anticipated medical cost savings would far exceed the cost of Roflex™ prescriptions and (2) there would be a significant improvement in patient health, compliance, productivity and quality of life.

1. ***OUR NOVEL PHARMACEUTICAL FORMULATION***

There is significant preclinical20,21 and clinical evidence22 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* respiratory18 and anxiety19 disorders. This cotreatment pharmaceutical formulation is based on decades of published scientific research20-24 and is the basis for two recently issued patents for respiratory disorders18 and anxiety disorders19 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 disorders18. In addition, this method can be used to directly reduce emotional and physical distress for individuals suffering from a variety of neuropsychiatric and neuro-developmental conditions, including chronic anxiety disorders.

Evidence suggests that selective cAMP-PDE4 inhibitors (e.g., roflumilast) are particularly potent agents for this cotreatment formulation18(pp.100-104),20,21. 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*.

1. ***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 cAMP20-22. 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 hyperalgesia20-22, similar to the noxious side effects of *exogenous* opioids (e.g., morphine, oxycodone)23,24.

Based on three decades of published preclinical research at Albert Einstein College of Medicine, Drs. Stanley M. Crain and Ke-Fe Shen discovered a simple method to switch opioid receptors from excessive *excitatory* signaling to normal *inhibitory* signaling23, which converts distress and hyperalgesia to calm and comfort when the receptors bind with either *exogenous* or *endogenous* opioids20--24. By adding an *ultra-low-dose* of an opioid receptor *antagonist* (e.g., naltrexone or naloxone) to an exogenous opioid receptor *agonist* (e.g., morphine or oxycodone), typical opioid side effects were significantly reduced and even reversed in both preclinical23 and large-scale clinical trials24. While other opioid receptor “switching” agents have been discovered (e.g., agents that increase sulfates, such as n-acetyl cysteine (NAC) and magnesium sulfate), *ultra-low-dose naltrexone* (ULDN) was the most specific, potent, and effective oral “*opioid receptor switcher*” found in these studies21.

More recent studies have applied these discoveries regarding the *bimodal nature of opioid receptors* to cAMP-PDE inhibitors20,21. 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 eliminated21. In fact, these noxious symptoms were *converted* to a *prolonged* state of calm, reduced reactivity to stress, and increased pain tolerance21. Moreover, given the potency of a selective cAMP-PDE4 inhibitor, *ultra-low-doses* of rolipram combined with ULDN, produced remarkably long-lasting distress relieving effects21.

Systematic studies have confirmed that these processes are mediated through the endogenous opioid system20,21 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 added20,21. 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 endorphins21,22. These studies found that selective cAMP-PDE4 inhibitors (e.g., rolipram) were particularly potent endorphin enhancers20-22.

***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)18(pp.93-96,99-104),21,22. In addition to non-specific cAMP-PDE inhibitors (e.g., theophylline, caffeine), the selective cAMP-PDE4 inhibitor roflumilast was also used18(99-104). Throughout these studies, participants often experienced at least some degree of emotional and/or physical distress, including anxiety, restlessness, malaise, and hyperalgesia, when taking a cAMP-PDE inhibitor alone18(pp.93-104),21,22. 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 energy18(pp.93-104),21,22.

Induced pain tasks, including a blinded “cold pressor” paradigm, were used to assess participants’ physical and emotional reactions to acute stress18((pp.93-96,101-104),21,22. When administered alone, cAMP-PDE inhibitors, such as roflumilast and theophylline, generally produced *hyperalgesia* reflected in *reduced* pain tolerance and *increased emotional distress*. In the “cold pressor” trials, the administration of PDE inhibitors alone led to an average *decrease* in pain tolerance of 12% from baseline, as compared to an average 7% *increase* produced by placebo. However, when the PDE inhibitor was combined with ULDN or NAC, participants experienced a remarkable *reduction* inboth *physical* and *emotional distress*, with *increased* average *pain tolerance* of 18% over baseline*, to the level of low-dose opioid pain medications*, yet with none of the noxious side effects typically experienced with these drugs18(pp.93-96,101-104),21,22.

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 anxiety18(pp.93-96,101-104),21,22. These clinical findings were similar to those shown in earlier preclinical studies27 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 months18(pp.99-101),21,22. The most effective formulation in these case studies was roflumilast combined with ULDN18(pp.100-101),22.

Since cAMP-PDE inhibitors are frequently used to treat respiratory disorders, co-treatment formulations of roflumilast or theophylline with ULDN were used effectively in case studies of six asthma patients with co-morbid anxiety, with remarkable respiratory and anxiolytic benefits over the course of a year-long trial18(p.101). The patients had previously tried conventional anxiety and/or depression medication, but discontinued due to side effects and lack of efficacy. Not only were the neuropsychiatric side effects of roflumilast and theophylline eliminated, but the patients also experienced remarkable anxiolytic and mood enhancing benefits in addition to improved control of their asthma18(p.101). Patients were much more able to handle stress in their lives, without experiencing asthma and/or anxiety attacks than ever before18(p.101). These preliminary case studies demonstrate the relative safety and effectiveness of Roflex™ in the treatment of respiratory disorders with co-morbid anxiety.

Therefore, these preliminary clinical studies confirm that the pharmaceutical combination of cAMP-PDE inhibitors, such as roflumilast, with ULDN has important clinical potential for the treatment of *both* respiratory and anxiety 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.

1. ***PROPOSED DRUG DEVELOPMENT PLAN***

We expect that our patented co-treatment pharmaceuticals will become the standard-of-care for most moderate-to-severe COPD and asthma patients since they have been developed to simultaneously reduce respiratory and emotional distress and dramatically decrease respiratory flare ups and exacerbations as well as improve patients’ quality of life.

Since the FDA has approved roflumilast for the treatment of COPD, it appears reasonable to focus the initial stage of our drug development program upon the clinical safety and efficacy of adding an ultra-low-dose of naltrexone (ULDN) to a therapeutic dose of roflumilast (Roflex™) for the treatment of COPD. Clinical trials using roflumilast alone (Daliresp®) could be used as comparison group. Outcome measures should include COPD exacerbations, anxiety and depression, quality of life, medication side effects, as well as frequency, level, and cost of medical services. Outcome for patients with diagnosed co-morbid anxiety/depression as compared to those without co-morbidity could be analyzed.

If clinical trials of Roflex™ are successful and FDA approval for COPD is granted, physicians would also be free to use this formulation, using clinical judgment, for asthma, which is also covered by the same patent. Since roflumilast alone has been shown to have clinical benefits for asthma, the emotional and physical distress relieving benefits of Roflex™ should be very beneficial for asthma patients as well. If Roflex™ proved successful in the treatment of asthma, additional clinical trials for this indication would be appropriate. Clearly, a significantly improved first in-kind pharmaceutical for respiratory disorders, which is expected to dramatically increase physician and patient acceptance and compliance, is likely to gain a significant share of the multi-billion dollar respiratory medication market.

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 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 Pharmaceuticals is seeking partnership and licensing agreements for this 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. For more information, please contact:

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