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AkPharma's Proposed Nasal Tissue-Protective Drug Carrier

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Calcium glycerophosphate for treating and preventing respiratory diseases and conditions

There are ~6000 approved drugs on the shelf. Some of them could be now be nasally administered under patent protection when utilizing NasoCell™ as a protective carrier.

AkPharma's cell-protective NasoCell spray will now allow many heretofore exclusively oral and IM drugs to be safely nasally administered.

The advantages to the patient over oral or IM administration can be substantive in ease of use, dose precision, time to act and non-compromise of medication integrity.

Executive Summary

Drugs administered orally are subject to first-pass hepatic metabolism, reducing bioavailability. Intramuscular or intravenous delivery, although almost instantaneous, is invasive and cannot always be self-administered. Intranasal delivery would be a promising alternative to both except for potential irritation of the nasal tissue by many pharmaceutical agents. There is a potential now for many older drugs to re-emerge as IP-protected, FDA-approved new-to-the-market drugs, based on their combination with NasoCell as the carrier or vehicle.

AkPharma Inc. has developed and patent-protected a novel non-drug nasal spray and drug carrier based on the GRAS (as food) molecule, calcium glycerophosphate (CGP), a compound with demonstrated effectiveness in the treatment and prevention of rhinitis. Its cell barrier-protective properties suggest potential patent-protected resurrection of a large number of the estimated 6000+ drugs long approved but off patent and heretofore excluded from intranasal administration.

CGP is not known to interact with other drugs and study data support the proposed uses described here. Several studies also support its use on its own as an effective rhinitis spray.

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AkPharma Inc. has discovered, developed and IP protected, a non-drug, non-saline nasal spray whose working name is NasoCell™. Its active ingredient is the small molecule, calcium glycerophosphate (CGP). Numerous urinary bladder, respiratory and intestinal tract uses for CGP have been discovered and substantiated by AkPharma.

NasoCell has the potential of becoming an important delivery vehicle for the intranasal administration of an array of drugs heretofore restricted via that route. Critically, as a generally recognized as safe compound, it can be expected to do no harm. It is believed to present no age barriers as to use. NasoCell speaks to an effectively unfilled market vacancy for a safe and uncomplicated nasal-protectant drug vehicle that could repurpose a number of the more than 6000 still useful older, longtime FDA-approved drugs, many off the market or of diminished profitability because of patent expiration. An estimated 80-90% of these drugs are of nasally-absorbable 1000Da or lower in size, suitable for intranasal delivery. Some of these have the potential to irritate the nasal mucosa. A combination of any those drugs with NasoCell would speak to that problem and would have patent protection. Because this method would work with any extant drug that is (a) of appropriate molecular size, and (b) irritating to nasal mucosa when repetitively applied, there is an impressive 'scale' promise in this innovation for the company controlling it.

Calcium glycerophosphate is a simple molecule with a multi-year history of use as a food ingredient, food acid neutralizer and cosmetic ingredient. It is listed in the Food Chemicals Codex (FCC) and Cosmetics Ingredient Review (CIR). AkPharma has played a major role in uncovering CGP's anti-inflammatory properties and has conducted over two dozen studies on its uses in skin care, wound healing and nasal applications. US Patent No. 9,861,647, January 18, 2018, covers AkPharma's proprietary uses of CGP for respiratory and drug carrier purposes, the focus of this disclosure.

Data from AkPharma studies with Caco-2 cells show that CGP alone does not change baseline barrier properties, as assessed by mannitol permeability and trans epithelial electrical resistance (TEER). However, it does prevent cytokine-induced increases in transepithelial permeability in a concentration-dependent manner. It can be expected that CGP alone will neither increase nor decrease the tightness of the nasal mucosal epithelium. However, the nasal mucosa may be irritated by components of a nasally administered preparation, an irritation mediated by cytokines derived from cells of the immune system. AkPharma's work showing that CGP prevents cytokine-induced increases in intestinal Caco-2 cells' permeability, suggests that CGP will mitigate irritation in nasal epithelium as well.

It is not anticipated that a CGP-content vehicle would be useful in facilitation of nasal absorption of molecules >1000 Da in the nasal cavity. It would be expected, however, to reduce nasal irritation following nasal administration of the large percentage of pharmaceutical agents that size and smaller, when co-presented as a carrier. This action may not be trivial. The number one reason for therapeutic failure is lack of patient compliance. If a patient becomes non-compliant because a nasally administered drug is irritating, he/she is not likely to be compliant. If, by reducing nasal irritation, CGP increases the likelihood of patient compliance, that is something worth commercial pursuit.

(1) Description of Product (NasoCell™): An aqueous solution/ suspension consisting of water, calcium glycerophosphate (3.0% suspension/0.75% solution), glycerin, sorbitol, and methyl and propyl paraben.

(2) Identity of Active Ingredient: Calcium glycerophosphate, CAS No. 27214-00-2, is an organic compound composed of calcium loosely bound to glycerophosphate. CGP dissociates under moist conditions and at suitable pH into calcium and glycerophosphate which are metabolized in the human body as nutrients. A portion of nasally-inhaled calcium glycerophosphate remains temporarily coated on nasal passages as the moisture carrier evaporates.

(3) Function of Inactive Ingredients: Glycerin and sorbitol are humectants, with sorbitol having the further properties of nasal coating, cooling and a slight sweetening. Methyl and propyl paraben are preservatives; other preservatives may be preferred.

(4) Observable Respiratory Actions: Formal laboratory animal studies and human clinical studies commenced July 2007 and continued through 2015. Results indicate that 2 daily applications to nasal passages via direct spray in human users subject to chronic nasal blockage/irritation, open the nose and lessen nasal mucus secretion and mucus related issues. Participants reported nasal passages open to more breathable state, remaining in open status for 4-8 hours. Additionally, lower airways were noticeably freer and more open. Repeated use over multiple weeks and months appeared to lead to an apparent break in nasal blockage/irritation/post-nasal drip cycles and permitted drop-off in usage frequency, with nasal openness and more comfortable breathing continuing for 24 hours and longer. Laboratory and clinical studies including objective measurements in both animals and humans support these observations. In one study (Schulman-Drexel) the subject with the greatest increase in breathing capacity was a previously diagnosed COPD patient.

Working Hypothesis of Mechanism of Action - Pharmacology: The nasal response to external irritants is partially governed by the signaling molecule, sphingosine-1-phosphate (S1P). As an established phosphatase inhibitor, CGP is believed to prevent destruction of S1P, consequently upregulating S1P concentrations. AkPharma's studies in Caco-2 cells have demonstrated that CGP increased cytokine-induced S1P in a time and concentration dependent manner, while simultaneously preventing cytokine-induced reductions in trans-epidermal electrical resistance (TEER) or increases in mannitol permeability. Alternatively, by inhibiting protein phosphatases, S1P may be inhibiting the inflammatory signaling cascade. Either could be the mechanism behind CGP's behavior as an anti-inflammatory and cell barrier protectant.

Size of product dose dispensed and "safety factor" considerations: When used in rhinitis: Spray application is a 200 mg spray containing 7.5 mg CGP +/- 1.5 mg per action from a squeeze-actuated, metered or non-metered bottle. Recommended usage: 2 sprays per nostril 2x to 3x per day = 8 - 12 sprays total per day. CGP content in solution: 3.75%, of which the amount in solution will not exceed 0.75%, with the balance, +/- 3.0% remaining as suspended particulate matter. Total CGP intake per day: 60 – 90 mg. Particulate CGP reaching the trachea and bronchi is expected to be trapped by the mucus layer, then propelled by the epithelial cilia lining the bronchi up to the pharynx and swallowed. Any CGP reaching the lung will be absorbed. Datta &

Weis (World J Gastroenterology 2015 Aug 14; 21(30): 9055-9066) demonstrated the ability of calcium glycerophosphate to act as a cell/cell adhesion enabler in the intestine, suggesting its similar role elsewhere in wet tissue. Earlier work by AkPharma supports the important role played by calcium glycerophosphate in wound healing.

Source/Safety/Regulatory Status: CGP for AkPharma's studies was produced in a modern plant in Hyderabad, India, and meets the criteria delineated in the Food Chemicals Codex for lead and other impurities. CGP is also available from a number of other quality sources, e.g., Seppic, in France. There are no known adverse drug interactions. In the present usage CGP is not a drug. AkPharma initiated the listing of CGP in the USP in November, 2007 as a dietary supplement. Based on direct contact with FDA, product regulatory status for nasal use is considered to be: "cosmetic – nasal wash." FDA presently regulates CGP in other applications. CGP has previously been used as an IM injectable CGP as a drug (Calphosan® - no longer marketed). It is a Generally Recognized As Safe (GRAS) dietary supplement. AkPharma investigated the use of CGP in oral tabular form for the treatment of interstitial cystitis (IC) in 2005 under an Investigational New Drug (IND) status (withdrawn).

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Nasal Study Abstracts: Applications of AkPharma's NasoCell™

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(1) Calcium Glycerophosphate Nasal Spray Reduces Rhinitis Symptoms; Schulman et al; Drexel University College of Medicine, Phila, PA

Rationale: Many patients with rhinitis remain symptomatic and/or intolerant of treatment. Recently, Baines *et al*. (2014) reported that ALP is elevated in neutrophilic asthma, leading us to hypothesize that a topical spray of calcium glycerophosphate (CGP), an ALP inhibitor, might be useful in treating rhinitis.
Methods: This study was approved by the Drexel University Human Research Protection Committee. Twelve subjects (37±4.7 YOA, 3M, 9 F) with target composite run-in scores ≥ 5 (0=no symptoms to 3=severe symptoms) for rhinorrhea, itching, congestion, and sneezing were treated with intranasal CGP (30 mg/nostril, b.i.d., as a spray) over 3 weeks. Subjects scored AM and PM pre and post treatment rhinorrhea, itching, congestion and sneezing for the three-week period of the study. Results, including pulmonary function tests, were assessed weekly and data analyzed by analysis of variance for repeated measures.
Results: The mean pre-treatment composite score was 7.24±0.465. The score declined significantly ($p<0.0001$) over the period of the study, to 3.88±0.684 (AM, pre), 2.53±0.453 (AM, post), 3.94±0.636 (PM, pre) and 2.57±0.480 (PM, post). There was a linear trend to increase FVC ($p=0.0112$), but not FEV1 or PEF. The mean WBC tended to decline over the course of the study from 7.38±0.58 x 103 to 6.67±0.52 x 103 ($p=0.0899$). Similarly, EOS tended to decline from 2.52±0.77% at run-in to 2.08±0.48% ($p=0.104$).
Conclusions: These data demonstrate that intranasal CGP effectively reduces the symptoms of rhinitis. More importantly, even in this very small study, treatment showed a trend to improve FVC. Both WBCs and EOS trended down from the upper to the midrange of normal, suggesting that treatment reduced the general state of inflammation. The CGP molecule is classified as

"generally recognized as safe" by the FDA. As a normal metabolic intermediate, it is unlikely to have significant abuse liability, even when used over a long period of time. These properties make it an attractive candidate for rhinitis treatment.

(2) 2014 Effects of AkPharma's Calcium Glycerophosphate Nasal Spray Wash (AkP 010112A) on Patient-Perceived Breathing Comfort; Lovelace Scientific Resources, Inc., Albuquerque, NM

EXECUTIVE SUMMARY

AkPharma Inc. has developed a calcium glycerophosphate (CGP) nasal spray wash for perceived rhinitis symptoms. The primary objective of the study is to assess subject nasal allergy symptoms. Also to be examined are changes in morning versus evening symptom scores and onset of the action of calcium glycerophosphate nasal spray, as well as changes observed in nasal eosinophil count and nasal histamine values. On study day 7, 14 and again at study day 21 subjects visit[ed] the study center where adherence to symptom diary and weight of the calcium glycerophosphate nasal spray wash is evaluated to confirm adherence. The secondary objective include[d] the changes observed in the FEV1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) on pulmonary function (spirometry) testing. Spirometry [observations were] repeated on study day 7, 14 and again at study day 21.

In general, the subjects recruited into the study had persistent mild to moderate symptoms at baseline prior to the onset of treatment. Upon treatment with calcium glycerophosphate there was an immediate improvement in all symptom categories after the first week of treatment. Average daily symptoms scores over the three weeks of treatment with AKP010112A were significantly improved from baseline levels (Table 1). There was improvement in Respiratory symptoms. Respiratory function was evaluated (FEV and FVC; reported as % of predicted) at baseline and day 7, 14, and 21. There were no significant differences between baseline measures and anytime during the course of treatment. In general, the reported adverse events were generally mild to moderate and did not require treatment. The most common adverse effects were stinging/burning immediately following treatment, nasal dryness, and sore throat. These events were most likely associated with the initial delivery of the calcium glycerophosphate. The preponderance of the subjects indicated on a satisfaction questionnaire that they would be willing to use/purchase this product in the future, thus indicating that it was generally well tolerated and provided some noticeable benefit.

(3) 2011 Acoustic Rhinometry and Pathologic Analysis on Ovalbumin-sensitized Guinea Pigs Treated With Calcium Glycerophosphate; Texas Tech University Health Sciences Center – Laboratory Animal Resources Center, Lubbock, TX.

ABSTRACT: The goal of this five-day study was to determine whether twice daily dosing of intranasal calcium glycerophosphate improves nasal congestion as measured by acoustic rhinometry, and to determine any histopathologic effects to brain, lungs and/or any organs or cells. Adult guinea pigs were sensitized by repeated exposure to chicken ovalbumin, then challenged on day 1 of the study to induce acute, allergic rhinitis. On each of days 1-5, human-dose equivalents were given twice daily of either calcium glycerophosphate, known OTC anti-

rhinitis drug, or placebo. The largest congestion-associated effect with calcium glycerophosphate treatment occurred on day 1 with significant improvement of nasal cavity volume over baseline ($p<0.05$). Days 2-5 showed definite trends toward improvement in nasal cavity volume in a dose-dependent manner that did not reach statistical significance ($p>0.05$). Exceptions to the trending observation existed on day 2 where the 1.875% CGP group (teal) performed as well as the 7.5% CGP group (green), on day 3 where the 1.875% and 3.75% CGP groups (teal and violet, respectively) outperformed the 7.5% CGP group (green), and on day 5 where the 3.75% CGP group (violet) outperformed the 7.5% CGP group (green). The 7.5% CGP group (green) trend either equaled or outperformed the known OTC anti-rhinitis drug on 4 of the 5 study days. Treatment with calcium glycerophosphate was well tolerated by the animals and no visible adverse clinical signs were observed including very low nose rub and sneeze counts during post-dosing observation. Blood counts and serum clinical chemistries showed only minor changes due to sensitization, and elevated serum IgE confirmed all treated animals had acute rhinitis. Tests of nasal lavage fluid including cell counts and inflammatory mediators showed no adverse effects of treatments. Tissue histopathologic analysis showed lesions confined solely to the nasal mucosa and were associated with experimental rhinitis. These representative lesions were not considered to be related to the test articles. Overall, the responses using calcium glycerophosphate treatment demonstrated improved nasal congestion in the guinea pig model of acute, allergic rhinitis and treatments were well tolerated by the animals.

(4) 2010 Effects of inhaled calcium glycerophosphate on Rhinitis Responses in Ragweed Sensitized Dogs; Lovelace Respiratory Research Institute, Albuquerque, NM

1.0 Executive Summary

The goal of the study was to determine whether repeated inhalation and intranasal instillation of calcium glycerophosphate attenuates ragweed induced nasal congestion and has an effect on nasal inflammation. Pretreatment with the compound at the dose achieved (1.6 mg inhaled and 30 mg intranasally instilled) significantly attenuated nasal congestion and had some minor effects on the early mediators measured in nasal lavage fluid collected for up to 60 minutes after nasal ragweed challenge. There was a general trend towards a reduction in some mediators (histamine, leukotrienes and prostaglandin D_2) but none reached statistical significance. When PGE_2 levels are normalized to baseline levels it suggests that there is a greater reduction following RW challenges in conjunction with calcium glycerophosphate treatment. This may suggest that PGE_2 is a potential underlying mechanism for the effects of calcium glycerophosphate. Compound pretreatment did reduce eosinophil numbers at day 2 post ragweed challenge but this did not reach statistical significance. Treatment with calcium glycerophosphate was well tolerated by the animals and no visible adverse clinical signs were observed nor any significant effects on blood chemistry parameters. Overall, the response seen following calcium glycerophosphate is similar to responses we have previously observed with an α-adrenergic agonist, pseudoephederine, a Histamine H1 antagonist, Chlorpheniramine, and Montelukast in this model.

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