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(54) Title: RECOMBINANT HUMAN CC10 AND COMPOSITIONS THEREOF FOR USE IN THE TREATMENT OF NASAL RHINITIS

(57) Abstract: The present invention relates generally to the use of recombinant human CC10 (rhCC10), also known as recombinant human uteroglobin, for use as a therapeutic in the treatment of nasal rhinitis, nasal sinusitis, chronic rhinosinusitis, and nasal polyposis. More particularly, the invention provides methods, including broadly the critical dosage ranges of rhCC10 and intranasal route of administration, which may be administered to safely and effectively treat the aforementioned conditions. The invention further provides a composition useful in administering rhCC10 to humans.

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# RECOMBINANT HUMAN CC10 AND COMPOSITIONS THEREOF FOR USE IN THE TREATMENT OF NASAL RHINITIS

## Cross-reference to Related Applications

This application claims benefit of and priority to, U.S. Provisional Patent Application 61/052,861, filed May 13, 2008, the disclosure of which is hereby incorporated by reference in its entirety.

## Field of the Invention

The present invention relates to methods of reducing airflow obstruction in the nasal passages, clearing a sinus infection, and reducing sinus pain in a patient. More specifically the present invention relates to methods of treating nasal rhinitis, sinusitis and nasal polyposis in patients and compositions useful for the same. Yet more specifically, the present invention relates to methods of treating the above using intranasally-administered recombinant human CC10 and compositions thereof useful for the same.

## Background

Clara Cell "10 kDa" protein (CC10) or uteroglobin (UG) is a small, homodimeric secretory protein produced by several mucosal epithelia and other organs of epithelial origin (Mukherjee, 1999). CC10 consists of two identical subunits of 70 amino acid residues, each with the "four helical bundle" secondary structure motif, joined in antiparallel orientation by two disulfide bonds between Cys 3 and 69', 3' and 69 (Matthews, 1994; Morize, 1997). The homodimer containing two disulfide bonds appears to be its primary, extracellular active form. In humans, the lung is the main site of CC10 production, while several other organs synthesize smaller amounts of mRNA encoding this protein (Singh, 1987; Sandmoller, 1994). CC10 is an anti-inflammatory and immunomodulatory protein that has been characterized with respect to various interactions with other proteins, receptors and cell types (reviewed in Mukherjee, 2007, Mukherjee, 1999, and Pilon, 2000). Lower levels of CC10 protein or mRNA have been found in various tissue and fluid samples for a number of clinical conditions characterized by some degree of inflammation including asthma (Lensmar, 2000; Shijubo, 1999; Van Vyve, 1995), pneumonia (Nomori, 1995), bronchiolitis obliterans (Nord, 2002), sarcoidosis (Shijubo, 2000), and in patients suffering from chronic rhinitis with recurrent sinusitis and nasal polyposis (Liu, 2004). Pulmonary

epithelial cells, the body's primary source for endogenous CC10, are often adversely affected in these conditions, depleted or even ablated (Shijubo, 1999). Indeed, CC10 appears to be an autocrine and/or endocrine required for development of specific sets of non-ciliated respiratory epithelial cells and associated structures (Castro, 2000). Thus, it is still not known whether CC10 deficiency is a cause or an effect of the inflammation and/or the condition.

The obstruction of airflow in the nasal passages, as well as sinus pain and pressure, are known to be causes of significant morbidity in humans suffering from allergic rhinitis, non-allergic rhinitis, sinusitis, and nasal polyposis. Nasal rhinitis is an inflammation of the nasal passages and sinuses in the nasopharygeal cavity. There are two types of rhinitis, allergic and non-allergic. Non-allergic rhinitis is due to viral, bacterial, or other infection, to exposure to inhaled chemicals or other irritants, or may be idiopathic, while allergic rhinitis is due to exposure to inhaled allergens. Allergic rhinitis may be seasonal, such as allergy to tree or grass pollen; or it may be perennial, such as allergy to dust mites and common molds. Rhinitis ranges in severity from mild seasonal discomfort due to itching, sneezing, and nasal discharge for a few hours, days or weeks, to painful and debilitating chronic sinus inflammation that is often associated with recurrent bacterial infection. Chronic sinus inflammation in the presence of bacterial infection is sometimes referred to as chronic rhinosinusitis ("CRS"). CRS, leads to irreversible remodeling and scarring of airway epithelia and sinus tissue. These permanent changes to the nasal tissues result in a vicious cycle in which decreased ability to fight infection, both viral and bacterial, as well as a decreased ability to clear inhaled allergens and irritants, lead to even more exaggerated inflammatory responses, further exacerbating remodeling and fibrosis, and more severe or persistent infections. Theoretically, inflammation is reversible in the absence of infection, and should disappear as soon as the irritant, pathogen, or allergen is cleared from the local tissue. Therefore, the transition from seasonal or mild rhinitis to CRS can be attributed largely to chronic exposure to perennial allergens and/or recurrent bacterial infection of the inflamed nasal and sinus tissue, leaving the infection to persist even after the original rhinitis stimuli (allergen or irritant) is long gone. Indeed, patients with perennial allergies resulting in chronic rhinitis often experience recurrent bacterial infection (sinusitis) as the inflammatory response transitions from an allergen-stimulated response to an infection-stimulated response. These are the patients with severe persistent rhinosinusitis CRS disease and the highest morbidity. Chronic rhinitis, whether allergic or non-allergic,

results in excess mucus production in, and swelling of, nasal passages that impairs breathing, disrupts sleep, and predisposes to repeated bacterial sinus infections. The sinus pain and pressure causes significant morbidity in this disease. Bacterial infection, whether acute or chronic, exacerbates these symptoms. In the most severe cases, nasal polyps grow in the nasal airways and slowly obstruct them. These polyps are non-malignant outgrowths of sinus tissue which can only be removed by sinus stripping surgeries. A patient with nasal polyps may undergo sinus stripping periodically since the polyps grow back after each removal.

However, determining whether rhCC10 can alleviate inflammation, and at what dosage, in patients suffering from nasal rhinitis, especially chronic rhinitis and rhinosinusitis, with or without nasal polyposis and in patients suffering from chronic or recurrent bacterial sinus infection has remained elusive. In fact, as shown below, recent work indicates that at dosages known and commonly used, rhCC10 is ineffective:

In a recent Phase II clinical study to evaluation the efficacy of intranasal rhCC10 to suppress nasal inflammation and rhinitis due to seasonal allergy, rhCC10 treatment resulted in a significant worsening of symptoms in one of six efficacy outcome measures compared to placebo (Widegren, et al., 2009). The remaining five efficacy outcome measures showed no difference between rhCC10 and placebo, although all trended in favor of placebo. RhCC10 was inferior to placebo in improving (increasing) peak nasal inspiratory flow and in mitigating rhinorrea caused by administration of aero-allergens. Table 1 shows comparative outcomes of patients while receiving rhCC10 versus outcomes in the same patients while receiving placebo, as measured during the last three days (days 5-7) of each treatment period.

Table 1: P-values for statistical differences between rhCC10 and placebo in five clinical outcome measures.

| Efficacy Variable | rhCC10 | Placebo | P-value |
|---|---|---|---|
| Morning TNSS | 1.64 (0.21) | 1.50 (0.25) | .57 |
| Morning PNIF | 136 (7) | 136 (8) | .78 |
| Evening TNSS | 1.37 (0.28) | 1.54 (0.27) | .53 |
| Evening PNIF | 145 (8) | 147 (8) | .93 |
| TNSS- 10 min after challenge | 5.67 (0.27) | 5.17 (0.32) | .09 |
| PNIF- 10 min after challenge | 93 (6) | 102 (7) | .04* |

* A p-value of < 0.05 (less than 0.05) is considered to be a significant difference.

P-values higher than 0.05 are not considered to be statistically significant.
TNSS: Total nasal symptoms score
PNIF: Peak nasal inspiratory flow

This proof-of-concept study failed to demonstrate the overall efficacy of rhCC10 given once daily for seven days in this nasal allergen challenge model of seasonal allergic rhinitis. RhCC10, given 1.1 mg in 200μL per day intranasally, did not favorably affect allergen-induced morning, post challenge or evening symptoms compared with placebo. A higher PNIF reflects greater airflow and a lower PNIF indicates restricted airflow. Morning as well as evening PNIF were unaffected by rhCC10, however, post challenge PNIF was modestly reduced by rhCC10 treatment compared to placebo, which did reach statistical significance. Symptom-scores and PNIF-levels reached in the placebo arm were very similar to those recorded historically in this model. Likewise, markers of inflammation in nasal lavage fluids, including levels of eosinophil cationic protein, myeloperoxidase, and alpha2-macroglobulin, and rhCC10 did not mediate any reduction in these markers compared to placebo. In this model, it has been demonstrated that corticosteroids inhibit morning, post-challenge as well as evening symptoms and these markers of inflammation in nasal lavages (Ahlstrom –Emanuelsson et al., 2002 & 2007) whereas anti-histamines reduce post-challenge symptoms only (Korsgren et al. 2007). Therefore, using this dose, dosing regimen, volume and spray method of intranasal administration, rhCC10 did not demonstrate anti-allergy, anti-inflammatory effects in all six clinical outcome measures or in all three inflammatory markers in nasal lavages.

Currently, most nasal rhinitis and rhinosinusitis are treated with various over-the-counter and prescription medications such as anti-histamines, decongestants, non-steroidal anti-inflammatory agents ("NSAIDS") and various non-pharmacologic nasal sprays

and irrigation solutions. Chromium nasal solutions, oral anti-histamines and leukotriene receptor antagonists treat symptoms but provide only a few hours of relief. Nasal oxymetazoline solutions are very effective at opening nasal passages but overuse results in a "rebound effect" and rapid loss of efficacy with worsening of symptoms. Side effects for these types of drugs include sore throat, dehydration of nasal tissues, and constipation, among others.

Furthermore, sinusitis is typically treated with oral antibiotics. Antibiotics range in side effects from mild to severe and can include constipation and other digestive problems, headache, dizziness, rashes, liver, kidney and bladder toxicity, muscle and joint pain, etc. Antibiotics can also cause hypersensitivity reactions, particularly in patients with recurrent sinusitis who have to take antibiotics repeatedly and eventually become allergic to them. Hypersensitivity reactions to antibiotics may occur without warning or previous signs of allergy and may be suddenly lethal.

For severe and/or chronic rhinosinusitis disease, physicians currently prescribe nasal corticosteroids, which reduce inflammation but often lose efficacy after a few weeks or months of continuous therapy. Oral corticosteroids are also efficacious but have many undesirable side effects when used for long periods of time. For example, in adults, cardiovascular complications, including hypertension and stroke, are major side effects of corticosteroid use. In children, corticosteroids impair normal growth and development. In all patients, corticosteroids lower the patient's immune function and leave them susceptible to infection of all types (bacterial, viral, fungal, etc.). Thus, safety is a major consideration in the choice of drugs and drug combinations used to treat, prevent or cure nasal rhinitis, especially chronic rhinosinusitis, nasal polyposis, chronic or recurrent bacterial sinus infection, their associated morbidities and other similar conditions.

There are several formulations, devices, and methods by which drugs may be administered intranasally to treat rhinitis, sinusitis, and rhinosinusitis. One method for administering local intranasal doses of drugs to the nasal passages and sinuses is the use of liquid drug formulations in spray bottle or spray pump devices that are converted to aerosols by being forced through a small aperture and sprayed into the anterior portion of the nasal cavity through each nostril.

Particle sizes generated by the aforementioned devices are in the 5-10 micron range, which maximizes delivery and local deposition of the drug in the nasal mucosa lining the nasopharygeal cavity. The nasal mucosa is comprised of a normally thin layer of mucus

that overlays the wet epithelium in the nasal passages and sinuses of the nasopharyngeal cavity. Most 5-10 micron particles sprayed into the nostril will impact the non-ciliated epithelium in the anterior portion of the nasopharyngeal cavity. Once deposited at the site of impaction in the nasal mucosa, drugs may distribute throughout the mucosa and be cleared at various rates through the action of cilia and ciliated epithelial cells located in the posterior two thirds of the nasopharyngeal cavity that push towards the pharynx where the drug and mucus are swallowed. The local action of drugs deposited in the nasal cavity depends upon the particle size delivered, the formulation, and the rate of clearance. These factors affect the efficiency of local delivery and the length of time that the nasopharyngeal mucosa and epithelia are exposed to the drug before it is cleared.

The local action of intranasally administered drugs also depends upon the condition of the nasal mucosa and tissues at the time of delivery. For example, when the nasal passages are blocked by thick mucus, local delivery of drugs is very difficult, if not impossible.

Therefore, it is a significant challenge to find an agent, and a correct dosage for that agent, which alleviates airway obstruction, sinus pain and discomfort for a prolonged period of time without serious side effects. There is therefore a need for new, more effective or longer-lasting agents and formulations thereof and administration and dosage regimens thereof, particularly in patients with chronic disease.

**Objects of the Invention**

The foregoing provides a non-exclusive list of the objectives achieved by the present invention:

It is a primary object of the invention to treat, cure or prevent nasal rhinitis, sinusitis, especially chronic rhinitis and rhinosinusitis, with or without nasal polyposis, in patients using rhCC10.

It is a further object of the invention to alleviate the pain and sinus pressure associated with chronic rhinitis, sinusitis, and rhinosinusitis using rhCC10.

It is a further object of the invention to enable patients with nasal rhinitis or sinusitis to achieve a better quality of sleep using rhCC10.

It is a further object of the invention to administer the rhCC10 to patients by intranasal instillation, nasal lavage or as an intranasal aerosol involving the use of a spray device.

It is a further object of the invention to provide a safe, well-tolerated and effective dosage range of rhCC10 which accomplishes the above objectives and does not significantly suppress the immune response or increase the frequency or severity of adverse events.

It is a further object of the invention to provide a drug-device combination by which rhCC10 can be effectively administered to the nasopharygeal cavity as an aerosol, as a gel, or as a liquid.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application in a gel or cream for local administration and prolonged release, using a single use swab applicator.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application as an aerosol with particles sizes in the 5-10 micron range for local administration and deposition, using a spray pump or squeeze bottle.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application as an aerosol with particles sizes in the 5-10 micron range for local administration and deposition, using a multi-use spray pump dispenser, metered dose inhaler (MDI), or squeeze bottle device.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application as an aerosol with particles sizes in the 1-5 micron range for pulmonary administration and deposition, using a single or multi-use spray pump dispenser, metered dose inhaler (MDI), or squeeze bottle device.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application as an instillation in a single or multi-dose syringe device.

It is a further object of the invention to provide a formulation of rhCC10 in specific pharmacologically-acceptable nasal excipients for application as an instillation in a nasal lavage solution using a “neti pot” or similar gravity flow lavage device.

It is a further object of the invention to provide rhCC10 itself as a pharmacologically-acceptable nasal excipient for the alleviation of pain, irritation, and discomfort caused by local inflammatory responses at the site of administration of other drugs in the nasopharyngeal cavity.

It is a further object of the invention to provide rhCC10 itself as a pharmacologically-acceptable nasal excipient to enhance the bioavailability of other drugs administered to or via the nasopharyngeal cavity.

It is a further object of the invention to provide rhCC10 as an active ingredient in combination formulations with other drugs for intranasal administration.

The term "pharmacologically-acceptable" is intended to characterize a formulation or combination of excipients that cause no deleterious effects or cause deleterious effects that are known and are, or can be, accepted by regulatory authorities.

**Summary of the Invention**

These and other objects, features and advantages are achieved by administering rhCC10 in a dosage range given at appropriate intervals, or in one dose, to treat, cure or prevent nasal rhinitis, sinusitis, rhinosinusitis, and CRS, with or without nasal polyposis. Furthermore, for chronic rhinitis patients rhCC10 offers an even greater benefit in treating, curing or prevention of chronic rhinitis when given in a dosage range at appropriate intervals, or in one dose. Thus, it has now been surprisingly found that rhCC10, which was thought to be ineffective in curing, treating or preventing nasal inflammation, rhinitis, nasal rhinitis, chronic rhinitis, sinusitis and rhinosinusitis, is in fact effective when used in accordance with the invention herein.

These and other objects, features and advantages are also achieved by administering rhCC10 in a dosage range given at appropriate intervals or in one dose where a patient shows one or more of the following: sinus pain and pressure, inability to sleep due to sinus discomfort, chronic rhinitis, rhinosinusitis, and growth or regrowth of nasal polyps.

These and other objects, features and advantages are also achieved by administering rhCC10 such that it does not inhibit platelet aggregation, suppress the immune response, such as in common cold or flu, or increase the frequency or severity of any adverse event.

In certain aspects of the invention, rhCC10 is administered intranasally in a single dose divided about equally between each nostril in a range of 1.5 micrograms to 1.1 milligrams per day, or in multiple doses which taken together achieve this dosage range on a daily basis to treat, cure or prevent severe nasal rhinitis, nasal sinusitis, especially chronic rhinosinusitis, and/or nasal polyposis. In another aspect, an intranasal rhCC10 dose or doses divided about equally between each nostril in a range of 1.5 micrograms to 1.1 milligrams per day can be repeated at appropriate intervals to treat, cure or prevent severe nasal rhinitis,

nasal sinusitis, chronic rhinitis with recurrent sinusitis, especially rhinosinusitis, and/or nasal polyposis. In yet another aspect of the invention, rhCC10 is administered intranasally on a daily basis consecutively for seven days, ten days, 14 days, or 21 days.

In yet another aspect of the invention, rhCC10 is administered three times per day, at approximately eight hour intervals in intranasal doses divided about equally between each nostril in a range of 0.5 to 370 micrograms per day. In yet another aspect of the invention, rhCC10 is administered two times per day, at approximately twelve hour intervals in intranasal doses divided about equally between each nostril in a range of 0.75 to 650 micrograms per day.

In yet another aspect of the invention, rhCC10 is administered in a tapered fashion, beginning with three times per day, at approximately eight hour intervals in intranasal doses divided about equally between each nostril in a range of 0.5 to 370 micrograms per day for three days, followed by two times per day, at approximately twelve hour intervals in intranasal doses divided about equally between each nostril in a range of 0.5 to 370 micrograms per day, followed by one time per day in intranasal doses divided about equally between each nostril in a range of 0.5 to 370 micrograms per day. In yet other aspect of the invention, rhCC10 is administered intranasally in accordance with the above aspects but in a dose or doses adding up to between about 15 nanograms and about 10 milligrams.

Whether administered intranasally or otherwise, rhCC10 can be given alone, in conjunction with, before or after other standard rhinitis and sinusitis treatments, including but not limited to intranasal or systemic corticosteroids, NSAIDs (including aspirin, COX-2 inhibitors), pain medications, antibiotics, antivirals, antifungals, decongestants, antihistamines, chromium solutions, nasal lavage, saline nasal lavage, and homeopathic remedies.

In another aspect, rhCC10 can be used as an excipient and/or local anti-inflammatory, and/or local immunosuppressor, to facilitate the local nasal delivery or application for local delivery or systemic absorption of other drugs to the nasal tissues that may or may not irritate or otherwise elicit, or may elicit, an undesired local irritation at the site of application. Thus, rhCC10 may be used as an excipient for other drugs to alleviate or avoid discomfort associated with nasal delivery.

In another aspect, rhCC10 can be used as an excipient or to alleviate the irritation caused by intranasal administration of other drugs for either local or systemic delivery.

In addition, rhCC10 can be formulated as an aqueous solution, a suspension (containing a nasal surfactant excipient), or a gel (such as a hydrogel employing, for example, hydroxymethylcellulose), in order to achieve the proper viscosity for nasal application and local distribution profile in the nasopharyngeal cavity. Likewise, rhCC10 can be formulated in combination with other active ingredients such as antibiotics or other antimicrobial agents, saline nasal lavages, decongestants, mucolytics, LTRA's, β-agonists, bronchodilators, etc.

In another aspect, rhCC10 is formulated as an aqueous solution that is loaded into a nasal spray squeeze bottle, metered dose inhaler or spray pump device. In yet another aspect, rhCC10 is formulated as a suspension in a surfactant that is loaded into a nasal syringe-type application device, a metered dose inhaler, or other nasal application device. Further, in still another aspect, rhCC10 is formulated in a hydrogel, or other form of artificial mucus, and single doses are placed in a single use nasal swab device for intranasal application.

## Detailed Description

The present invention relates to the critical dosages and timing of administration of rhCC10 to treat, cure or prevent nasal rhinitis and sinusitis, especially chronic nasal rhinitis with recurrent sinusitis, chronic rhinosinusitis, and nasal polyposis in humans. The rhCC10 is preferably obtained by the processes described in U.S. Patent Application Publication Nos. US 2003-0109429 and US 2003-0207795 attached hereto at Ex. A & B, respectively, both of which are incorporated by reference in their entirety, or via any other process which yields pharmaceutical grade (meeting FDA requirements) rhCC10. The rhCC10 of the embodiments of the present invention can be administered with, without, before or after other intranasal, pulmonary, or systemic therapy.

## Dosages

Preferably, in treating or preventing nasal rhinitis, sinusitis, chronic rhinosinusitis, and nasal polyposis, rhCC10 is administered intranasally, to each nostril 1-3 times per day, for 7-14 days, and every other day thereafter for another 14 days, and thereafter as needed. More preferably, rhCC10 is administered as soon as the patient begins to experience sinus pain and pressure.

To effectuate the desired outcomes which are further described below, reference is made to methods of administration described in the following embodiments:

In one embodiment, a dose or multiple doses of rhCC10 equaling a dose ranging from about 1.5 micrograms to about 1.5 milligrams can be administered. In another embodiment, rhCC10 can be administered in the dose range on a daily basis. In yet another embodiment, rhCC10 can be administered in the dose range on a daily basis for at least seven days consecutively. In still a further embodiment, rhCC10 can be administered in the dose range on a daily basis for at least 14 days consecutively. In still another embodiment, rhCC10 can be administered in the dose range every other day for 30 days consecutively. In yet another embodiment, rhCC10 can be administered in tapered dosages daily for ten consecutive days, said tapered dosages comprising a high dose at each administration for the first three days, an intermediate dose at each administration for the second three days, and a low dose at each administration for the last four days. In yet still another embodiment, rhCC10 can be administered in the dose range or in tapered doses up to three times per day, approximately every eight hours.

In another embodiment the above doses of rhCC10 can be administered intranasally to the patient. In yet another embodiment, the above doses of rhCC10 can be administered to the patient as an aerosol, by intranasal instillation, or by deposition of a gel or cream in nasal passages. In a further embodiment, rhCC10, in accordance with the methods described above, can be administered prior to, during or after an oral or intranasal decongestant, anti-histamine, corticosteroid, mucolytic, expectorant, mucus suppressor, surfactant, bronchodilator, vasoconstrictor, sinus pain analgesic, or other typical therapy. In still another embodiment, rhCC10, in accordance with the methods described above, can be administered to treat or prevent nasal rhinitis, nasal sinusitis, chronic rhinosinusitis, or nasal polyposis in a patient.

The doses of rhCC10 and application methods described above can be administered daily, more than once daily, three times daily, every other day or in a tapered fashion depending upon the severity of disease being treated, the patient's overall health, and whether an acute or chronic condition is being treated. For example, the more severe the disease condition, the higher the amount of rhCC10 would be required to effectively treat the disease. For maintenance therapy of chronic disease, for example, to prevent an exacerbation of nasal rhinitis, nasal sinusitis, or nasal polyposis, lower doses would be used. It is understood that a physician would be able to monitor and adjust doses, formulations,

and application methods as needed based on the patient's symptoms and responses to therapy and within the parameters and dose ranges described in the embodiments of the present invention.

**Formulations**

rhCC10 is maximally effective when applied directly to the local nasal epithelium, for example by use of a liquid formulation in a spray bottle, spray pump, or lavage. Therefore, it is sometimes necessary to use fast-acting local mucolytics, anti-histamines, and/or decongestants, as well as physical methods such as inhaling moist warm air, hot compresses applied to the face, and salt water nasal lavage to open up the nasal passages before rhCC10 can be applied effectively to the nasal epithelia.

Intranasal instillation is another method for administering rhCC10 that can be accomplished using rhCC10 in either a liquid or gel formulation. The gel dosage formulation provides the advantage of better local dosing over a longer period of time by retaining the dose of rhCC10 in the local nasal area in which it was swabbed longer, whilst liquid dosages may be partially swallowed following instillation due to normal nasal drainage resulting in much shorter local exposures and smaller local doses. However, intranasal instillation of a liquid dosage form by nasal lavage, using a "neti pot" type of device, confers the advantage that the dose is more immediately distributed over a larger surface area in the nasal tissues and sinuses, than a local application gel formulation.

rhCC10 can be formulated with several nasal excipients for intranasal delivery. These include excipients to adjust the pH of the drug, to buffer the drug to maintain solubility, to act as preservatives or enhance preservatives for prevention of microbial growth and/or transfer, to adjust the tonicity, solubility, or viscosity of the drug, to enhance penetration or permeation of the drug (systemic delivery), to modify the local bioavailability and half-life of the drug (increase viscosity), to reduce toxicity, to suspend insoluble drugs, and to alter the taste of the formulation. Table 2 contains a non-exclusive list of exemplary excipients and their functions in intranasal formulations of rhCC10. Any single excipient or combination of excipients can be used to formulate rhCC10 for intranasal administration.

Table 2 : Examples of Excipients for Intranasal Formulations

| Excipient | Function |
|---|---|
| Acids (hydrochloric, acetic, citric) | pH adjustment, buffer |

| | |
|---|---|
| Sodium hydroxide | pH adjustment |
| Sodium & potassium salts (Sodium acetate, sodium citrate, sodium phosphate, potassium phosphate) | Buffer |
| Edetate disodium | Preservative enhancer, Metal chelator |
| Benzalkonium chloride | Preservative |
| Benzethonium chloride | Preservative |
| Benzyl alchohol (aka phenylcarbinol, etc.) | Preservative |
| Chlorobutanol | Preservative |
| Methylparaben | Preservative |
| Phenylethyl alcohol | Preservative |
| Phenylmercuric acetate | Preservative |
| Propylparaben | Preservative |
| Thimerosal | Preservative |
| Sodium or potassium chloride | Adjust tonicity (make isotonic) |
| Microchrystalline cellulose | Adjust viscosity |
| Na carboxymethylcellulose | Adjust viscosity |
| Hydroxyethylcellulose | Adjust viscosity |
| Ethanol | Solvent |
| Glycerol | Solvent/ Adjust tonicity |
| Glycine | Solvent/ Adjust tonicity |
| Dextrose | Adjust tonicity |
| Polyethylene glycol (PEG) | Solvent |
| Propylene glycol | Solvent |
| Glyceryl dioleate | Solvent |
| Glyceryl monoleate | Surfactant / emulsifier (suspend lipophilic drugs) |
| Lecithin | Surfactant / emulsifier (suspend lipophilic drugs) |
| Polysorbate 20 & 80 (aka Tween 20 & 80) | Surfactant / emulsifier (suspend lipophilic drugs) |
| Triglycerides | Multiple |
| Menthol | Modify flavor |
| Saccharin sodium | Modify flavor |
| Sorbitol | Modify flavor |
| Chitosan | Permeation enhancer |
| Cyclodextrin | Permeation enhancer |
| Bile salts | Permeation enhancer |
| Liposomes | Permeation enhancer |
| Starch microspheres | Permeation enhancer |
| Glycerrhizin | Permeation enhancer |

rhCC10 can also be formulated in combination with other drugs, artificial mucus, or other active ingredient for intranasal administration. Drugs with which rhCC10 can be formulated for intranasal administration include, but are not limited to, local or

systemic antimicrobial agents (antivirals, antibacterials, antifungals), decongestants, anti-histamines, mucolytics, expectorants, leukotriene receptor antagonists, bronchodilators, $beta_2$-adrenergic receptor agonists, local-acting vasoconstrictors (such as oxymetazoline), anti-inflammatory agents, and analgesic agents. Still other drugs with which rhCC10 can be formulated for intranasal administration for local or systemic effects include anti-inflammatory agents, $beta_2$-adrenergic receptor agonists, anti-cancer agents, anti-angiogenic agents, anti-fibrotic agents, immunomodulatory agents, vaccines, metabolic agents, analgesics, neuroleptic agents, anesthetics, agents for depression and other psychiatric disease (mental health), anti-addiction agents, homeopathic remedies, herbal preparations, vitamins and minerals and the like.

rhCC10 is compatible with most non-reactive chemicals and drugs, including hydrophilic and hydrophobic chemicals, nucleic acids and nucleic acid analogs, proteins and peptides, carbohydrates, lipids and phospholipids, etc. As a secretoglobin critically involved in transport of substances in epithelial cells, rhCC10 is ideally suited to enhance the delivery of other drugs via the nasal passages. rhCC10 can also act as a local anti-inflammatory agent that can be used as an excipient to suppress painful local nasal responses at the site of administration of other drugs, such as, for example, chemotherapeutic agents and drugs that produce a "burning sensation" upon administration.

A key parameter relevant to drug efficacy associated with intranasally administered rhCC10 is the concentration of the rhCC10 itself. Formulations in which the rhCC10 concentration is too high (i.e. above 2 mg/ml) have demonstrated null or even detrimental effects, as evidenced by the clinical outcomes described in the Background. The rhCC10 formulation was 5.6 mg/ml and was applied directly to the patient's nostrils (Widegren, et al. 2009). Conversely, in example 4, in which the rhCC10 concentration was 250-262 micrograms/ml, a clinical benefit was conferred. In an unrelated experiment, pre-term lambs treated with 5 mg/kg of body weight using a 5.5 mg/ml formulation of rhCC10, administered by intratracheal instillation, suffered from severe hypoxia and ¾ animals died of respiratory failure within four hours of drug administration, while none of the four placebo treated animals died (unpublished; Ikegami, M., Univ of Cincinnati). In contrast, when the same formulation of rhCC10 was diluted to 2 mg/ml and administered via intratracheal instillation to intubated pre-term lambs, the animals showed various benefits from receiving the drug compared to placebo (Miller, 2005a, 2005b, 2007; Shashikant, 2005). Without being bound to any particular theory, the phenomenon may be related to the

very high sphere of hydration for rhCC10, that is, the number of water molecules coordinated by CC10 is higher than the average protein. Administration of high concentrations of CC10 to mucosal and other bodily fluids may result in the "subtraction" or loss of water from the local fluids, thereby causing a local dehydration and detrimental disruption in the equilibria between substances in the local biological milieu. Alternatively, or in conjunction with the preceding, an acute local over-abundance of CC10 may also result in desensitization of cells and tissues to the presence of CC10, effectively reducing the potency of the drug rather than increasing the pharmacologic effect. In some cases, feedback inhibition of a pathway or set of pathways involving a particular metabolite or mediator may actually result in the opposite effect (activation versus suppression and vice versa) than may be observed at lower doses of the metabolite or mediator. A cutoff for rhCC10 formulations intended to be administered to nasal and other mucosal surfaces by intranasal, intratracheal or other local/topical administration is 2 mg/ml, above which rhCC10 is not efficacious and can even be detrimental.

The following detailed examples are illustrations of embodiments. It should be clear that these are not intended to limit the scope of the present invention.

## EXAMPLE 1

### Intranasal Administration of rhCC10 to Allergic Rhinitis Patients

RhCC10 was produced in E. coli bacteria and purified by a process (Claragen, Inc., College Park, MD), described in U.S. Application Publication Nos. US 2003-0109429 and US 2003-0207795, both of which are incorporated by reference in their entirety. The protein for the study was provided as a >98% pure solution of recombinant human CC10 homodimer. The biological activity of each batch was compared using a proprietary secretory $PLA_2$ inhibition assay, described in U.S. Application Publication Nos. US 2002-0169108 which is incorporated herein by reference.

In the nasal allergen challenge model, patients with known seasonal allergies to known allergens were subjected to instillation of an allergen solution into the nasopharyngeal cavity on seven consecutive days. In order to minimize safety risks the amount of allergen instilled was carefully calibrated in each patient to elicit a mild local allergic response that is quantitated using four main outcome parameters over the seven day challenge period. These parameters include; 1) total nasal symptom scores, 2) peak nasal inspiratory flow, 3) quantitation of biomarkers in nasal lavages, and 4) response to histamine challenge.

A total of 35 patients with seasonal allergies to tree pollens completed a placebo-controlled, randomized, blinded, cross-over nasal allergen challenge study of rhCC10 versus placebo at the Lund University Hospital in Lund, Sweden. The purpose of the study was to determine the safety, tolerability and efficacy of intranasal administration of recombinant human Clara Cell 10 kDa (rhCC10) protein in subjects with allergic rhinitis. In order to investigate whether intranasal administration of rhCC10 could mitigate the nasal rhinitis symptoms caused by nasal allergen challenge.

Patient responses to nasal allergen challenges in the absence of rhCC10 were first measured and baseline data recorded. A total of 39 patients were screened for inclusion in the study. All patients were male subjects, aged 18-50 years, with Body Mass Index between 18 and 28 $kg/m^2$, and a history of birch and/or timothy pollen-induced seasonal allergic rhinitis for at least the previous 2 years and otherwise healthy. Each patient had elevated specific IgE or at least one positive skin prick test (SPT) to at least one aero allergen (eg. timothy or birch pollen) and each patient exhibited symptoms provoked by the allergen with a corresponding elevated specific IgE or positive SPT. Subjects were excluded from the study if they had perennial allergy (e.g. chronic rhinitis), except for cat and/or dog sensitivity under the condition that these subjects are not exposed to cats and dogs. Subjects were also excluded if they had other nasal disease (eg. structural abnormalities of the nose, rhinosinositis, or nasal polyposis), any upper respiratory tract infection during the period of 2 weeks before the start of the study, were currently receiving treatment or had received treatment within 4 weeks of enrolment with intranasal, inhaled or systemic glucocorticosteroids, β2-adrenergic receptor agonists, or any other anti-inflammatory medication, or had a bacterial or fungal infection within the past month prior to enrollment. A summary of patient characteristics and baseline data is given in Table 2.

**Table 2. Summary of Demographic and Baseline Data**

| | | |
|---|---|---|
| Age (years) | Mean (SD) | 26.1 (5.5) |
| | Range | 19 - 48 |
| Race | Caucasian | 39 |
| Gender | Male | 39 |
| Body weight (kg) | Mean (SD) | 81.1 (10.3) |
| Height (cm) | Mean (SD) | 182.6 (7.2) |
| Body mass index (BMI) | Mean (SD) | 24.3 (2.53) |
| Systolic blood pressure | Mean (SD) | 121.4 (9.2) |
| Diastolic blood pressure | Mean (SD) | 77.4 (5.9) |

| | | |
|---|---|---|
| Pulse rate | Mean (SD) | 68.8 (8.2) |
| Ear, nose and throat | Normal | 38 |
| | Abnormal | 1 |
| Cardiovascular | Normal | 39 |
| Respiratory | Normal | 39 |

Patients were initially screened for their responses to tree pollen allergens to determine the amount of allergen administered during the challenge periods which was calibrated based on individual patient responses. A physical examination was given, including ear, nose and throat examination and vital signs. Then a nasal allergen challenge was performed in order to establish the allergen dose which resulted in at least 5 sneezes and/or a symptom score of at least 2 on a scale of 0 – 3 for either the symptoms of nasal congestion or rhinorrea. Rhinorrea is defined as a discharge from the nasal mucus membranes and is typically watery. All allergen administrations were performed in the clinic by hospital staff. In order to estimate, for each individual, the symptom-producing, tolerable, and repeatable allergen dose for the nasal challenge series, a titration procedure was performed in all subjects. The allergen (birch or timothy pollen) that induced the most significant wheal reaction in the skin prick test was chosen for the nasal titration. Increasing doses of allergens (Alutard®, ALK, Denmark) was administered at 10-min intervals using a nasal spray-device. The spray-device delivered 100 µl per actuation, and one puff was sprayed into each nostril resulting in effective doses of 100, 300, 1000, and 3000 SQ-Units per nasal cavity. This scheme was followed until the patient responded acutely with at least five sneezes and/or a symptom score of at least 2 or more on a scale from 0 to 3 for either of the symptoms nasal blockage and runny nose. The allergen dose that produced this effect was chosen for the daily allergen challenge series during the first and second treatment periods (eg. cohorts.) The type and amount of allergen administered to each patient is shown in Table 3.

**Table 3. Selection of allergen and number of sneezes at allergen titration per subject**

| Subject | Selection of allergen (Histamine /Birch ) | 100 SQ-Units | 300 SQ-Units | 1000 SQ-Units | 3000 SQ-Units |
|---|---|---|---|---|---|
| **1** | Timothy | 6 | - | - | - |
| **2** | Timothy | 3 | - | - | - |
| **3** | Timothy | 0 | 0 | 0 | 0 |

| Subject | Selection of allergen (Histamine /Birch ) | 100 SQ-Units | 300 SQ-Units | 1000 SQ-Units | 3000 SQ-Units |
|---|---|---|---|---|---|
| **4** | Timothy | 1 | 1 | 4 | 6 |
| **5** | Timothy | 0 | 2 | - | - |
| **6** | Timothy | 0 | 0 | 0 | - |
| **7** | Timothy | 1 | 5 | - | - |
| **8** | Timothy | 3 | 4 | 0 | - |
| **9** | Birch | 0 | 4 | - | - |
| **10** | Timothy | 10 | - | - | - |
| **11** | Timothy | 0 | - | - | - |
| **12** | Timothy | 0 | 3 | - | - |
| **13** | Timothy | 0 | 0 | - | - |
| **14** | Birch | 3 | 7 | - | - |
| **15** | Timothy | 0 | 1 | - | - |
| **16** | Timothy | 1 | - | - | - |
| **17** | Timothy | 2 | 5 | - | - |
| **18** | Timothy | 3 | 0 | - | - |
| **19** | Birch | 0 | 0 | 0 | - |
| **20** | Timothy | 0 | 0 | 4 | - |
| **21** | Timothy | 4 | 4 | - | - |
| **22** | Timothy | 3 | - | - | - |
| **23** | Birch | 1 | 10 | - | - |
| **24** | Birch | 3 | - | - | - |
| **25** | Birch | 4 | 4 | - | - |
| **26** | Birch | 0 | - | - | - |
| **27** | Timothy | 4 | 2 | - | - |
| **28** | Timothy | 0 | 0 | 0 | - |
| **29** | Birch | 0 | 0 | 0 | 1 |
| **30** | Timothy | 9 | - | - | - |
| **31** | Timothy | 11 | - | - | - |
| **32** | Timothy | 1 | 1 | 2 | - |
| **33** | Birch | 0 | 0 | 2 | - |
| **34** | Timothy | 2 | 2 | - | - |
| **35** | Timothy | 6 | - | - | - |
| **36** | Timothy | 1 | 7 | - | - |
| **37** | Timothy | 0 | 3 | - | - |
| **38** | Birch | 0 | 5 | - | - |
| **39** | Timothy | 0 | 0 | 3 | - |

The study was performed during the pollen-free winter months. The study was blinded and placebo-controlled in that doctors and patients were not aware of whether they were receiving rhCC10 or placebo. The study was randomized in that patients were randomly assigned to either the rhCC10 or placebo treatment groups. The study was cross-over design in that each patient was treated in two seven day cohorts separated by a washout period of 3-5 weeks. Each patient completed a cohort in which they received rhCC10 and one in which they received placebo. Patients were allowed to take several types of non-steroidal medications, as needed, to relieve their nasal and sinus discomfort during the

treatment period. Analgesics (including aspirin but not ibuprofen) and antibiotics were allowed, and Clarityn®(Claritin™) 10 mg, was allowed in case of severe allergic symptoms and was provided by the clinic.

The test agents, placebo and rhCC10, were placed in 10 ml glass vials, labeled numerically so that doctors and patients in the clinic would not be able to distinguish between them. A key was maintained in the hospital pharmacy and doctors were to be informed of the identity of each vial only in the event of an adverse event in which the doctor would need the information to treat the patient. A disposable medical nasal spray device, manufactured by Valois Pharm (France), was connected to the 10 mL vials at the clinical site just before administration. This device consisted of a pump (VP7/100S 18PH), an actuator (PR147) and a cap (B25/A). Placebo consisted of sterile, unbuffered 0.9% sodium chloride. The rhCC10 was in sterile unbuffered 0.9% sodium chloride at a concentration of 5.6 mg/ml. Both placebo and rhCC10 appeared as clear, colorless, odorless liquids that could not be readily distinguished. A total of 100 microliters of placebo or rhCC10 was administered to each nostril of each patient on each day of treatment for a total of seven consecutive days of treatment in each treatment period. All allergen and test agent administrations were performed in the clinic by hospital staff. The total daily dose of rhCC10 was 1.1 milligrams per day, administered in a single dose as an aerosol sprayed in a 100 microliter volume to each nostril, or 0.56 milligrams per nostril. The rhCC10 was administered 15'-30' prior to administration of allergen.

The outcomes were measured as follows:

1. TOTAL NASAL SYMPTOM SCORE (TNSS)

Nasal symptoms, including nasal congestion, rhinorrea and sneezy/itchy nose were scored by the patients and recorded in the patient diary prior to administration of study medication in the morning (rating symptoms during the preceding 12 h, but disregarding possible symptoms the first 15 minutes post study medication). TNSS was recorded 15 minutes after each allergen challenge. In addition, symptoms were scored in the evening (again reflecting symptoms, during the preceding 12 h, excepting symptoms directly post dosing). The symptoms were each scored according to the following: 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms. The scores were added to constitute a total score, per time point, which ranged from 0 to 9. Mean nasal symptom scores, for morning

recordings, for recordings 10 minutes after allergen challenge, and for evening recordings, respectively, of the last three days of each allergen challenge period was used in the statistical analysis.

2. Peak Nasal Inspiratory Flow (PNIF)

PNIF was measured by the patients before the intake of the drug in the morning, 10 minutes after the allergen challenge, and in the evening. The measurements were carried out using a PIF-meter (Clements-Clarke, Harlow, U.K.) equipped with a facial mask. Patients stood up during the procedure, placed the mask snugly over the face with both hands, closed the mouth and inhaled through the nose. They recorded the value and returned the device to a reading of 30, then repeat the procedure 2 more times. The highest value of the three measurements was recorded in the diary. Similar to the nasal symptom score, PNIF recordings, per time point, of the last three days of each allergen challenge period were used in the statistical analysis.

## EXAMPLE 2:

## Co-administration of Medications

A total of ten patients in both the placebo and rhCC10 groups required rescue medications to treat their discomfort and allergy symptoms while on the protocol. As can be seen from Table 5, a variety of local and systemic drugs for relief of intranasal symptoms were taken, including anti-inflammatory agents, allergy medications, anti-histamines, corticosteroids (Flutide), and oxymetazoline.

Table 5: Co-administration of rescue medications in patients receiving placebo or rhCC10

| Subject | Treatment | Day | Medication (trademark / INN) |
|---|---|---|---|
| 3 | rhCC10 | 2 | Clarityn®(Claritin™)/loratadin |
| | | 6 | Clarityn®(Claritin™)/loratadin |
| | | 7 | Neseril / oximetazolin |
| 3 | placebo | 4 | Clarityn®(Claritin™)/loratadin |
| 5 | rhCC10 | 5 | Loratadin/ loratadin |
| 6 | placebo | 2 | Alvedon/ paracetamol |
| 12 | placebo | 3 | Loratadin/ loratadin |
| 13 | placebo | 3 | Loratadin/ loratadin |
| 15 | placebo | 3 | Loratadin/ loratadin |
| 18 | placebo | 5 | Clarityn®(Claritin™)/loratadin |
| | | 6 | Loratadin/ loratadin |
| 25 | rhCC0 | 1 | Alvedon/ paracetamol |
| | | 5 | Loratadin x2 / loratadin |

| Subject | Treatment | Day | Medication (trademark / INN) |
|---|---|---|---|
| | | 7 | Flutide Nasal/ flutikason |
| 25 | placebo | 7 | Antihistamin intake after evening PNIF |
| 26 | rhCC10 | 5 | Loratadin/ loratadin |
| | | 6 | Loratadin/ loratadin |
| 38 | rhCC10 | 5 | Clarityn®(Claritin™)/loratadin |
| | | 7 | Kestine/ ebastin |

Loratadin is a non-sedating antihistamine, paracetamol, is an analgesic and antipyretic, flutikason (fluticasone) is a corticosteroid anti-inflammatory agent, oxymetazoline is a selective alpha-1 agonist and partial alpha-2 agonist topical decongestant, and ebastin is a non-sedating $H_1$ antihistamine. These patients did not experience any significant AEs as a result of co-administration of these other agents simultaneously with the rhCC10, therefore, the combination of rhCC10 with these drugs is safe and pharmacologically-acceptable.

## EXAMPLE 3

### Safety and Tolerability of Intranasal Adminstration of rhCC10

As part of the safety assessment for this proof of concept intranasal administration of rhCC10 in humans adverse events (AEs) and serious adverse events (SAEs) were monitored, recorded and reported. The clinical investigator was responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. An AE is any untoward medical occurrence in a subject or a clinical investigation temporally associated with the use of the investigational drug whether or not the event is considered to have a causal relationship with the drug. In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form) was not reported as an AE unless the condition worsened or episodes increased in frequency during the AE reporting period. Serious adverse events were defined as any untoward medical occurrence that, at any dose; 1) results in death, 2) is life-threatening, 3) requires hospitalization or prolongation of an existing hospitalization, 4) results in disability/incapacity, 5) is a congenital anomaly/birth defect, 6) is an important Other Medical Event (OME), and 7) all grade 4 laboratory abnormalities. The AE reporting period for began upon receiving the first dose of investigational

medication and ended at the 2-week post discontinuation of investigational medication visit (follow-up visit).

No SAE's occurred during the study. Overall, a total of 15 adverse events were reported in subjects in both the placebo and rhCC10 treatment groups. All AEs were rated as mild in severity. In each group, 11 of 15 AEs were rated as non-assessable with respect to relatedness to study drug while four of 15 AEs in each group were rates as unlikely to be related to study drug. A summary of AEs for each patient receiving placebo is given in Table 6 and for those receiving rhCC10 at the time of the AE are given in Table 7.

**Table 6. List of adverse events for patient receiving placebo**

| Patient number | Description | Maximum intensity | Reported as serious? | Relationship to trial drug |
|---|---|---|---|---|
| 6 | Headache | 1 = mild | 0 = No | 1 = unlikely |
| 12 | Gastric influenza | 1 = mild | 0 = No | 4 = not assessable |
| 12 | Gastric influenza | 1 = mild | 0 = No | 4 = not assessable |
| 15 | Ear pain | 1 = mild | 0 = No | 1 = unlikely |
| 15 | headache | 1 = mild | 0 = No | 4 = not assessable |
| 15 | fatigue | 1 = mild | 0 = No | 4 = not assessable |
| 15 | ear pain | 1 = mild | 0 = No | 4 = not assessable |
| 20 | Sore throath | 1 = mild | 0 = No | 4 = not assessable |
| 20 | Common cold | 1 = mild | 0 = No | 4 = not assessable |
| 25 | Headache | 1 = mild | 0 = No | 1 = unlikely |
| 26 | Sore throat | 1 = mild | 0 = No | 4 = not assessable |
| 27 | stomach ache | 1 = mild | 0 = No | 1 = unlikely |
| 29 | common cold | 1 = mild | 0 = No | 4 = not assessable |
| 31 | Fever | 1 = mild | 0 = No | 4 = not assessable |
| 38 | urticaria | 1 = mild | 0 = No | 4 = not assessable |

Table 7: List of adverse events for patient receiving rhCC10

| Patient number | Description | Maximum intensity | Reported as serious? | Relationship to trial drug |
|---|---|---|---|---|
| 1 | Common cold | 1 = mild | 0 = No | 4 = not assessable |
| 2 | Common cold | 1 = mild | 0 = No | 1 = unlikely |
| 2 | Common cold | 1 = mild | 0 = No | 1 = unlikely |
| 7 | Sore throat | 1 = mild | 0 = No | 1 = unlikely |
| 16 | fatigue | 1 = mild | 0 = No | 4 = not assessable |
| 16 | fatigue | 1 = mild | 0 = No | 4 = not assessable |
| 23 | Headache | 1 = mild | 0 = No | 4 = not assessable |
| 23 | Common cold | 1 = mild | 0 = No | 4 = not assessable |
| 26 | Common cold | 1 = mild | 0 = No | 4 = not assessable |
| 28 | tired | 1 = mild | 0 = No | 4 = not assessable |
| 28 | tired | 1 = mild | 0 = No | 4 = not assessable |
| 28 | headache | 1 = mild | 0 = No | 4 = not assessable |
| 32 | Headache | 1 = mild | 0 = No | 4 = not assessable |
| 38 | ague | 1 = mild | 0 = No | 4 = not assessable |
| 39 | Mild cold | 1 = mild | 0 = No | 1 = unlikely |

Therefore, intranasal rhCC10 administration was found to be safe and well-tolerated in humans when given once daily as an aerosol in a divided dose of 1.1 milligrams, 0.56 milligrams per nostril, for seven consecutive days.

## EXAMPLE 4

### Intranasal Administration of rhCC10 to a Patient with Chronic Rhinitis and Recurrent Sinusitis (aka Chronic Rhinosinusitis)

An 11 mg (2 mls) aliquot of rhCC10 was added to a soft plastic squirt bottle containing 42 mls of sterile 0.65% saline containing disodium and monosodium phosphate, and phenylcarbinol (preservative) plus benzylkonium chloride (preservative), or 0.1% thimerosol (also a preservative), creating a 250 microgram/ml solution of rhCC10. The patient self-administered the rhCC10 by inserting the applicator end of the bottle to the nose, such that the aperture that dispenses the drug is held inside the nostril, and simultaneously squeezing and inhaling. A simple aerosol is created when the bottle is rapidly squeezed, forcing liquid through a small pinhole at the top of the nasal applicator end. The volume and dose delivered depends upon the rapidity of the squeeze and force exerted. Volumes ranging from 25-500 microliters, corresponding to 6.6-131 micrograms of rhCC10, are typically

dispensed. When the squeeze is harder and larger volumes are delivered, the nasal passages are lavaged and part of the dose may be swallowed or flow into the trachea over a period of several minutes.

In this example, rhCC10 was administered to a patient suffering from episodic and/or chronic sinus pain due to chronic rhinosinusitis, stemming from perennial allergies, with recurrent bacterial sinus infections. The patient's history includes; 1) antibiotics prescribed from two to twelve times per year for sinus infection in the past six years, 2) intranasal corticosteroids prescribed and taken as needed for the past six years, and 3) non-prescription analgesics, decongestants and anti-histamines taken daily to relieve sinus pain, nasal and chest congestion, and enable the patient to sleep through the night. RhCC10 was a useful substitute and adjunctive therapy for the patient in the following doses, dosing regimen, formulations, and drug-device combinations.

In the first dosing regimen, the patient suffered from a painful bacterial sinus infection for three days prior to self-administering the rhCC10 from the squirt bottle, with two squirts per nostril, three times per day for three days. The total daily dose intake using this method ranged from 78.6-1,572 micrograms total (39.3-786 micrograms per nostril), corresponding to 1.1 micrograms/kg – 22.5 micrograms/kg of body weight per day in the average 70 kg patient. The patient then tapered the dosing down to twice per day for two days (52.4-1,024 micrograms daily total (26.2-512 micrograms per nostril), corresponding to 749 nanograms/kg – 14.6 micrograms/kg per day in the average 70 kg patient), and then to once per day for two days (26.2-524 micrograms daily total, corresponding to 374 nanograms/kg – 7.5 micrograms/kg per day in the average 70 kg patient). After one week of tapered dosing regimen with intranasal rhCC10, the patient discontinued use. The patient's sinus pain, rhinitis and bronchitis symptoms (nasal congestion, sneeze, cough, airway constriction and chest congestion), and sleeplessness, disappeared within 24 hours of initiation of treatment and did not return for at least six weeks following the final dose of rhCC10. Intranasal rhCC10 was safe and well tolerated in the patient, although some drying of nasal mucous membranes was experienced.

## EXAMPLE 5

### Intranasal Administration of rhCC10 to a Patient to Prevent Recurrent Sinusitis

In a second dosing regimen, the patient received rhCC10 in the formulation and spray bottle of Example 4, twice per day, in the morning and evening, starting within 12 hours of sensing the first sinus pain. The sinus pain was associated with the recurrence of a

bacterial sinus infection that had been treated for 14 days with a powerful broad-spectrum antibiotic (eg. Levaquin), during which time the pain abated, but returned within four days of ending the antibiotic. Known side effects associated with the antibiotic occurred in the patient, including constipation and irritable bowels, chest pain, dizziness, transient numbness and tingling in the extremities, extreme sunburn, and increased susceptibility to bruising. As a result, the doctor advised the patient to avoid further use of the antibiotic. The patient then used rhCC10 with over-the-counter decongestants to treat the symptoms associated with the recurrent sinus infection. Within 24 hours of the first dose, the nasal pain and congestion disappeared. The patient continued to administer the rhCC10 twice per day for one week, then decreased to once per day for one week, then discontinued therapy. The bacterial infection did not recur for at least six weeks following intranasal rhCC10 therapy.

**EXAMPLE 6**

**Intranasal Administration of rhCC10 for Maintenance**

Maintenance therapy with rhCC10 to prevent sinus pain and infection, often arising from seasonal or perennial allergy and exposure to airborne allergens, is also possible. Daily intranasal administration of rhCC10, at a formulation concentration not to exceed 500 micrograms/ml (preferably not to exceed 250 micrograms/ml), in doses of 26.2-524 micrograms total, given in single or multiple actuations per nostril, corresponding to 374 nanograms/kg – 7.5 micrograms/kg of body weight) for up to two and one half months would safely control chronic rhinitis symptoms, rhinosinusitis, nasal and chest congestion, sinus infection and pain, and sleeplessness, and prevent the need for antibiotics, analgesics (NSAIDS such as aspirin, ibuprofen), decongestants, anti-histamines, and sleep-inducing drugs.

Using these methods, formulation, dose, dosing regimen, and drug-device combinations, rhCC10 was efficacious in the alleviation of symptoms associated with chronic rhinitis and bacterial sinus infection (aka chronic rhinosinusitis). In still other instances of severe or recurrent sinus infection, several other antibiotics (Amoxicillin, Zithromax, Biaxin, etc.) were used to contain bacterial growth while rhCC10 alleviated the pain and symptoms. For mild infections and to prevent severe painful infections, rhCC10 was used without an antibiotic, thus, sparing the patient the negative side effects associated with the antibiotic. No adverse events were associated with potential interactions between rhCC10, decongestants, antihistamines, and antibiotics. Thus, over the counter decongestants and antihistamines and antibiotics commonly prescribed for nasal sinusitis

were either avoided entirely or used safely in conjunction with rhCC10 to alleviate moderate to severe nasal symptoms.

## EXAMPLE 7

### Intranasal administration of rhCC10 for treatment of corticosteroid-refractory, antibiotic resistant, acute sinus infection

The patient suffered from a severe ongoing sinus infection, characterized by pain, pressure, disruption of sleep, loss of blood pressure upon standing, and inability to walk. The patient had no allergies to airborne allergens (seasonal or perennial) and the infection occurred in the month of January when no seasonal allergens were present. The diagnosis and severity of the sinus infection was verified by CT scan. Prior to receiving rhCC10, the patient had been on antibiotics for 5 weeks (amoxicillin; 500 mg/day; 10 days; then augmentin, 4 grams/day for 3 weeks) and on intranasal corticosteroid treatment for 10 days (fluticasone propionate). Despite these treatments, he remained in considerable pain, with pressure throughout his sinuses, and facial edema (puffiness). Immediately prior to receiving rhCC10, both sides of his nasal septum were blood red and contained readily visible dilated capillaries, indicating the presence of severe local inflammation. A 250 microgram/ml solution of rhCC10 in 0.65% saline containing disodium and monosodium phosphate, phenylcarbinol (preservative) and benzylkonium chloride (preservative) was then administered in a single intranasal dose as a spray into each nostril at a dose of approximately 20-50 micrograms per nostril. Approximately 12 hours after receiving the single intranasal dose of rhCC10, his nasal septum was a normal dusky purple with no dilated capillaries visible, indicating a profound local anti-inflammatory effect. The patient continued on rhCC10, twice daily, for 7 days, noting decreased sinus pain and pressure symptoms. The dosing regimen of rhCC10 was to be tapered from two squirts per nostril, twice per day for 3 days, to one squirt per nostril twice per day for 3 days, to one squirt per nostril once per day for 3 days. The patient continued with this regimen for 4 days. However, it was noted on day 5 that the patient still had intense pain in the ethmoid sinus, which is difficult to access with a nasal spray. Thereafter, the rhCC10 was administered on the same schedule by a lavage technique to increase access of rhCC10 to the surfaces of the ethmoid sinus region. In the lavage method, a total dose of 250 micrograms of rhCC10 (i.e. 1 ml of the 250 microgram/ml solution) was added to 118 mls (½ cup; 4 fluid ounces) of a standard commercially available nasal lavage solution. The patient received the lavage in the supine position with head tilted back, allowing the rhCC10 formulation to settle in the

sinuses for 3-5 minutes. The patient then sat up, allowing the lavage to flow out and be expelled by nose blowing. The lavage was administered twice per day for 2 days, then once per day for 3 days, then discontinued. A CT scan performed 21 days after the initial dose of rhCC10 revealed complete resolution of the sinus infection without evidence of scarring, epithelial thickening, or other remaining blockage. The rhCC10 formulation mediated a potent anti-inflammatory response, which was caused by a bacterial infection and not allergy. rhCC10 further mediated an anti-inflammatory response when standard anti-inflammatory therapy in the form of intranasal corticosteroids failed. rhCC10 also facilitated clearance of the bacterial infection, which resolved without the use of additional antibiotics. Finally, rhCC10 mediated a complete recovery of the nasal epithelia, avoiding the scarring, fibrosis, and epithelial thickening that typically accompanies such severe infections.

**EXAMPLE 8**

**Intranasal formulation of rhCC10**

Intranasal delivery of rhCC10 is useful for example, when treating upper respiratory (nasal and sinus and upper airway) inflammation and fibrosis, due to perennial allergy, infection, or some other form of acute or chronic upper respiratory irritation. rhCC10 is soluble in a wide range of aqueous solutions, over a wide range of pH values , for example 3.9-8.5, and in a wide range of salt concentrations (for example 0.1%-4%), as well as a variety of alchohol/water mixtures (for example 0.1%-90% ethanol). Thus, rhCC10 has the solubility and stability characteristics, to be used with a wide range of intranasal dispensing devices, including, but not limited to, for example, simple squirt bottles with uncontrolled volumetric doses for self-administration of liquid aerosols, pump-action or pressurized canister metered dose devices for self-administration of liquid aerosols, propellant-driven dry powder or liquid aerosol metered dose devices for self-administration, gel-laden nasal swabs for topical delivery to the nasal passages, and drug-loaded syringes for deeper topical administration and sinus lavage, for voluntary or involuntary administration to the conscious or unconscious patient.

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Based on the foregoing, the critical ranges for rhCC10 dosages effective to safely treat, cure and prevent nasal rhinitis, especially non-allergic rhinitis, nasal sinusitis, chronic rhinosinusitis, and nasal polyposis have been found. Accordingly, the present invention provides a safe and well-tolerated intranasal rhCC10 based therapy effective at treating the symptoms of nasal rhinitis, especially non-allergic rhinitis, nasal sinusitis,

chronic rhinosinusitis, and nasal polyposis thus reducing the significant morbidities in child and adult patients suffering from these conditions, while not causing any dangerous side effects.

In the Claims

1. A safe and well-tolerated method of treating rhinosinusitis in the nasal passages of a patient comprising: administering rhCC10 to the patient.
2. The method of claim 1 wherein the amount of rhCC10 administered is between about 1.5 micrograms and about 1.5 milligrams per day.
3. The method of claim 1 wherein the amount of rhCC10 administered is less than about 1.1 milligrams per day.
4. The method of claim 1 wherein the amount of rhCC10 that is administered is about 0.75 micrograms to about 650 micrograms per day.
5. The method of claim 1 wherein the amount of rhCC10 that is administered is about 0.5 micrograms to about 370 micrograms per day.
6. The method of claim 1 wherein the administration of rhCC10 is repeated about three times per day.
7. The method of claim 1 wherein the administration of rhCC10 is repeated about two days.
8. The method of claim 1 wherein rhCC10 is administered to the nasal passages by instillation, lavage, swab applicator, or spray.
9. The method of claim 1 wherein rhCC10 is administered in combination with an antibiotic, an anti-histamine, a decongestant, a mucolytic, an analgesic, a local-acting vasoconstrictor, a leukotriene receptor antagonist, a steroid, a nasal excipient, or any combination thereof.
10. A safe and well-tolerated method of preventing or slowing growth or regrowth of nasal polyps in a patient comprising: administering rhCC10 to the patient.
11. The method of claim 10 wherein rhCC10 between about 1.5 micrograms and 1.5 milligrams is administered each day for at least 2 days.
12. The method of claim 10 wherein the amount of rhCC10 that is administered is 1.1 milligrams per day or less.
13. The method of claim 10 wherein the administration of rhCC10 is repeated about three times per day.
14. The method of claim 10 wherein rhCC10 is administered to the nasal passages by instillation, lavage, swab applicator, or spray.

15. The method of claim 10 wherein rhCC10 is administered in combination with an antibiotic, an anti-histamine, a decongestant, a mucolytic, an analgesic, a local-acting vasoconstrictor, a leukotriene receptor antagonist, a steroid, a nasal excipient, or any combination thereof.

16. A safe and well-tolerated method of treating or preventing chronic or recurrent bacterial sinus infection in a patient comprising: administering rhCC10 to the patient.

17. The method of claim 16 wherein rhCC10 between about 1.5 micrograms and 1.5 milligrams is administered each day for at least 2 days.

18. The method of claim 16 wherein the amount of rhCC10 that is administered is 1.1 milligrams per day or less.

19. The method of claim 16 wherein the administration of rhCC10 is repeated about three times per day.

20. The method of claim 16 wherein rhCC10 is administered to the nasal passages by instillation, lavage, swab applicator, or spray.

21. The method of claim 16 wherein rhCC10 is administered in combination with an antibiotic, an anti-histamine, a decongestant, a mucolytic, an analgesic, a local-acting vasoconstrictor, a leukotriene receptor antagonist, a steroid, a nasal excipient, or any combination thereof.

22. A safe and well-tolerated method of treating sinus pain in a patient comprising: administering rhCC10 to the patient.

23. The method of claim 22 wherein rhCC10 between about 1.5 micrograms and 1.5 milligrams is administered each day for at least 2 days.

24. The method of claim 22 wherein the amount of rhCC10 that is administered is 1.1 milligrams per day or less.

25. The method of claim 22 wherein the administration of rhCC10 is repeated about three times per day.

26. The method of claim 22 wherein rhCC10 is administered to the nasal passages by instillation, lavage, swab applicator, or spray.

27. The method of claim 22 wherein rhCC10 is administered in combination with an antibiotic, an anti-histamine, a decongestant, a mucolytic, an analgesic, a local-acting vasoconstrictor, a leukotriene receptor antagonist, a steroid, a nasal excipient, or any combination thereof.

28. A pharmaceutical composition for intranasal administration of rhCC10 comprising a formulation containing rhCC10 in combination with a nasal excipient.

29. The pharmaceutical composition of claim 28 comprising rhCC10 at a concentration no greater than 2 milligrams/milliliter.

30. The pharmaceutical composition of claim 28 comprising rhCC10 at a concentration of 250 micrograms per milliliter in 0.65% sodium chloride, disodium phosphate, phenylcarbinol, monosodium phosphate, and benzalkonium chloride at a pH of 4.0-8.0.

31. The method of claims 1, 10, 16, and 22 wherein rhCC10 is administered in the pharmaceutical composition of claim 29 in a dosage of 20-50 micrograms per nostril up to four times per day.

32. A drug-device combination composition comprising the pharmaceutical composition of claim 30 and a squeeze spray bottle, pump action spray device, metered dose nasal actuator, syringe-type instillation device, nasal swab applicator, or "Neti pot" lavage device that enables the topical application of rhCC10 to the surfaces of the nasal passages.