CLINICAL PROTOCOL

Protocol No. 15-001CA

Title: An Open Label, Pilot Study Evaluating the Efficacy and Safety of the Use of Nasal Carbon Dioxide for the Treatment of Cluster Headache

Version:

Original	10 March 2015
Amendment 1	30 November 2015
Amendment 2	28 April 2016

Sponsor: Dr. Timothy Smith
Clinvest Research, LLC.
3805 South Kansas Expressway, Suite B
Springfield, MO 65807
Phone: 417-883-7889

Approval:

Investigator Printed Name	**Signature**

_____

Date

TABLE OF CONTENTS

1.0 STUDY SYNOPSIS

Title of Study:	An Open Label, Pilot Study Evaluating the Efficacy and Safety of the Use of Nasal Carbon Dioxide for the Treatment of Cluster Headache
Sponsor:	Dr. Timothy Smith Clinvest Research LLC 3805 South Kansas Expressway, Suite B Springfield, MO 65807 Phone: 417-883-7889
Indication:	For the treatment of cluster headaches in adults.
Primary Objectives:	To evaluate the safety and efficacy of nasal CO_2 for the treatment of cluster headache.

Study Design:

This is an open label, investigator-sponsored, pilot study. Subjects agreeing to participate in the study and meeting the eligibility criteria assessed at the screening visit will be enrolled in the study. The length of time between screening and treatment will last between 0 days to a maximum of 12 weeks. Subjects who enter the screening phase during a cluster headache episode and meet the study eligibility criteria can immediately enter the treatment phase and may opt to treat their cluster headache episode in the clinic. Subjects who are not in a cluster headache episode, who meet initial screening eligibility criteria, can remain in the screening phase for up to 12 weeks until their next cluster episode begins. Upon initiation of a cluster headache episode, subjects will enter the treatment period. Subjects will be trained on the proper use of the hand-held dispenser containing CO_2 calibrated to deliver 0.5 standard liters per minute (SLPM). This dispenser will be provided for use in the clinic or home. Subjects will be instructed to use the nasal CO_2 dispenser, 10 seconds/nostril, as needed up to 6 times to treat one attack. Each dose must be separated by 3-5 minutes. Subjects should treat only one attack in a 24-hour period. Subjects may treat up to three cluster headache attacks during the treatment phase of this study. One hour after the first dose, subjects can choose to treat with investigator-approved rescue medication. Subjects will be asked to complete an online diary after the completion of the dosing. Diary assessments will collect pain severity (0=none, 1=mild, 2=moderate, 3=severe), symptoms (such as tearing, nasal congestion, and running nose), nasal CO_2 usage, acute medication usage, satisfaction of treatment, number of cluster attacks, and unusual symptoms. Subjects will be contacted by phone within 3 days of the first use of the nasal CO_2 dispenser to assess adverse events (AEs) and medication usage. A total of 25 subjects will enter the treatment period and be instructed to treat up to 3 cluster headaches with nasal CO_2. Within 7 days of treating their last cluster headache episode, subjects will return for an end of study visit.

Number of Subjects: Up to 25 subjects enrolled and treating up to 3 cluster headaches in one cluster headache period.

Study Population: Subjects must meet all of the following **inclusion criteria** to be considered eligible for study entry:

1. Male and female, 18 years of age and older.
2. History of cluster headache, as defined by International Classification of Headache Disorders (ICHD), third edition, beta version guidelines (ICHD-3 beta, Cephalalgia 2013).
3. Stable on concomitant medications, excluding those for the treatment of cluster headache, for at least 60 days prior to enrollment.
   Note: Subjects are allowed to use their usual standard of care for the preventative treatment for their cluster headache. Acute/abortive medications maybe used 60 or more minutes after the initial dose, limited to the following: triptans; high-flow oxygen.
4. If female and of childbearing potential, have a negative urine pregnancy test at the time of Screening.
   a. To not be considered childbearing potential a subject must be surgically sterile, have had a hysterectomy or tubal ligation, post-menopausal for at least 1 year, or otherwise incapable of pregnancy.
5. Capable of completing online headache diary with access to internet.
6. Able to provide written Informed Consent.

Study Population (Cont'd): Subjects must not meet any of the following **exclusion criteria** to be considered eligible for study entry:

1. Recent nasal/midface trauma (< 3 months)
2. Recent nasal/sinus surgery (< 3 months).
3. Severe respiratory distress in the last 6 months.
4. Neoplasm such as Angiofibroma, sinus tumor, granuloma.
5. Nasal congestion present more than 10 days with fever (temperature ≥ 100.4 °F) and nasal mucous is an abnormal color.
6. Surgery to treat cluster headache.
7. History of aneurysm, intracranial hemorrhage, brain tumors or significant head trauma.
8. Structural intracranial or cervical vascular lesions that may potentially cause headache attacks.
9. Other significant pain problems (including cancer pain, fibromyalgia, and trigeminal neuralgia) that might confound the study assessments in the investigator opinion.
10. Psychiatric disorder, which in the opinion of the Investigator, may interfere with the study.
11. Pregnant, actively trying to become pregnant, or breastfeeding, and/or is unwilling to use an accepted form of birth control.
12. Skin around and inside the nasal passage that is dry, cracked, oozing, or bleeding.
13. Recurrent nose bleeds, which in the opinion of the Investigator, may interfere with the study.
14. Is participating in any other therapeutic clinical investigation or has participated in a clinical trial and received treatment in the preceding 30 days.

Investigational Product:	0.17 L CO_2 delivered through two 10 second administrations in each nostril, up to 6 times, to treat one attack (total of 1.0 L CO_2). Subjects may treat up to three cluster headache attacks during the treatment phase of this study (total of 3.0 L CO_2).
Efficacy Evaluation:	**Primary Endpoints:** Greatest change from pre-treatment headache pain intensity to post treatment at any time point within 30 minutes of Nasal CO_2 administration. **Secondary Endpoints:** • Percentage of subjects experiencing headache pain freedom at 5-60 minutes within the treated attack • Percentage of subjects with headache relief at 5-60 minutes within the treated attack • Rescue medication usage for treated attack • Subject satisfaction • Cluster recurrence
Safety Evaluation:	Safety assessments will include: • Monitoring adverse events (AEs) • Concomitant medications
Statistical Methods:	Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for each of the primary and secondary outcome measures will be statistically analyzed for within group changes via a 2-tailed repeated measures ANOVA and or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests.

Schedule of Events:

Study Procedures	Screening	Treatment	End of Study Visit[1]
Informed Consent	X		
Eligibility	X		
Medical History/ Medications / Demographics	X		
Physical Examination with Neurological and Nasal Mucosal Exam	X		X
Vital Signs	X		X
Urine Pregnancy Test	X		X
Subject Training	X		
Subject eDiary, AE/ConMed diary, and Questionnaire Instruction	X		
Investigational Product Dispensation	X	X[2]	
Accountability of Investigational Product and Study Supplies	X		X
Diary Completion		X	
Adverse Event Assessment		X	X
Concomitant Medications Assessment	X	X	X
Telephone Contact		X[3]	X
eSource Document and eCRF Completion	X		X

[1] The End of Study Visit should occur within 7 days after the subject treats up to his/her third headache or within 7 days after the completion of the 84-day treatment period, whichever occurs first.

[2] Subjects will return to the clinic at 4 and 8 weeks after Screening Visit as necessary for a replacement dispenser.

[3] Subjects will be contacted by telephone within 3 days of treating their 1st attack to answer any questions, assess if there are any problems with compliance or any concerning AEs.

2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AR	Allergic Rhinitis
ºC	Degrees Celsius
CDDS	Carbon Dioxide Drug Delivery System
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene-Related Peptide
CO_2	Carbon Dioxide
CRF	Case Report Form
ECG	Electrocardiogram
EU	European Union
ºF	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H^+	Proton
H_2CO_3	Carbonic Acid
HCO_3^-	Bicarbonate
ICH	International Conference on Harmonization
ICHD-II	International Classification of Headache Disorders-II
IHS	International Headache Society
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
L	Liter
MedDRA®	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs

Abbreviation or Term	Definition/Explanation
NSAE	Non-Serious Adverse Event
PAR	Perennial Allergic Rhinitis
pCO_2	Partial Pressure of Carbon Dioxide
PE	Physical Examination
pH	Log of the Hydrogen Ion Concentration
PP	Per Protocol Population
SAE	Serious Adverse Event
SAR	Seasonal Allergic Rhinitis
Sec	Second
SLPM	Standard Liters Per Minute, flow rate measured at a standard condition (25 °C and 1 bar)
TMD	Temporomandibular Disorder
TNSS	Total Nasal Symptom Score
TSA	Transportation Security Administration
US	United States
WHO-DRL	World Health Organization-Drug Reference List

3.0 BACKGROUND

3.1 Investigational Product

Capnia, Inc. is developing nasal, non-inhaled carbon dioxide (CO_2) for the symptomatic relief of diseases which may be mediated by the trigeminal nerve, including acute migraine and allergic rhinitis. Carbon dioxide, the active pharmaceutical ingredient, is CO_2 at $\geq$ 99.0% volume.

Carbon dioxide is a naturally occurring gas that readily diffuses across body tissues and membranes. Although the exact mechanism of action(s) of CO_2 is unknown, in vitro studies with cultured neurons have shown that CO_2 reduces intracellular pH while simultaneously suppressing neuropeptide secretion, in particular calcitonin gene-related peptide (CGRP).[1] It is hypothesized that upon application to the nasal mucosa, CO_2 diffuses into local tissue and upon interaction with water, forms carbonic acid (H_2CO_3), which subsequently releases a proton (H^+) and bicarbonate (HCO_3^-). The locally-released protons cause a drop in local tissue pH, which leads to depolarization and subsequent inactivation of local neurons. The inactivation of neurons likely coincides with inhibition of the release from the trigeminal nerve of CGRP and other inflammatory mediators implicated in the pathogenesis of migraine and other trigeminally-mediated diseases.

3.2 Cluster Headache

Cluster headache is a seriously debilitating disorder with 14 million individuals worldwide currently seeking treatment.[2] Characterized by recurrent bouts of excruciating unilateral pain with accompanying ipsilateral autonomic symptoms such as lacrimation, conjunctival erythema, nasal congestion, rhinorrhea, and occasionally a partial Horner's syndrome.[3] Cluster headaches typically last between 15-180 minutes with 75% of attacks lasting less than 60 minutes if left untreated.[4] They occur at a frequency of several times per day to several times a week with a cluster period typically lasting 8-12 weeks.

Cluster headaches are classified separately from migraine on the basis of more severe pain, more frequent attacks, shorter duration of attacks, different autonomic symptoms, and a different underlying pathophysiology. Interestingly, while migraine headaches are more commonly diagnosed in women, cluster headaches are up to 3 times more prevalent in men.[3,4] Currently, the etiology cause of cluster headaches is not fully understood, however, there has been an increased interest in the role of the sphenopalatine ganglion (SPG) and trigeminal ganglion in cluster headache.[6] Both of these ganglion innervate the sinuses and offer a potential therapeutic target for the treatment of cluster headache. Current standard of care treatments included both abortive and prophylactic medications; both with limited efficacy. During the onset of headache, many people respond to high flow oxygen and triptans have been shown to reduce severity and duration of attack, although do not demonstrate long-term prophylactic effects.

The social and economic burden of cluster headache is significant. Patients with chronic and active episodic cluster headache are severely impacted in non-economic and economic of their lives. A study by D'Amico et al found a 36% of cluster headache patients have lost their jobs and half the patients have reduced work time by at least 50%.[7]

Considering the inadequacy of current pharmacological therapy at considerable economic and social burden of this debilitating disorder, further research is warranted on alternative treatment options.

3.3 Non-Clinical and Clinical Data

This section provides a brief summary of non-clinical and clinical data obtained to date. Additional Pharmacology/Toxicology as well as clinical safety information are summarized in the Investigator's Brochure. Toxicology studies have been conducted in rats as well as rabbits. Preliminary data is summarized in the Investigator's Brochure.

3.3.1 *In Vitro* Non-Clinical Evaluations

Experiments in primary cultures of rat trigeminal ganglia showed that CO_2 treatment of culture under isohydric conditions (i.e., buffered to prevent extracellular acidification), significantly suppressed the stimulatory effects of various stimuli on CGRP release.

These experiments provide evidence of a potentially unique mechanism of action by which CO_2 inhibits sensory nerve activation and subsequent release of CGRP.[1]

3.3.2 *In Vivo* Non-Clinical Evaluations

Experiments in a hyperalgesic rat model have shown normalization of withdrawal latency of experimentally-induced ear pain with the administration of nasal CO_2. Subsequent experiments reported that this effect was decreased to a small extent if the duration of CO_2 administration was decreased by half the time, but there was a much more significant decrease in the anti-hyperalgesic effect if the flow rate was decreased by half.[8]

These experiments show that CO_2 had an anti-hyperalgesic effect in non-clinical models of pain, and that flow rate may be a significant determinant of the magnitude of this effect.

3.3.3 Clinical Evaluation in Healthy Volunteers

Study C011 was a randomized, double-blind, placebo-controlled study in healthy human volunteers designed to assess the tolerability of nasal CO_2 at different flow rates (0.22 L/min and 0.44 L/min) and using different nosepieces (direct versus indirect flow). Twenty-three subjects

were assigned to receive combinations of high or low flow rate (and placebo) with each type of nosepiece.

In C011, the most common AEs reported were related to the administration site (described in different terms such as nasal discomfort, tingling, burning, pain, stinging, irritation, etc.), lacrimation, rhinalgia, ear/nose/throat discomfort or pain, unusual/unpleasant taste, headache, and rhinorrhea. Additional AEs reported were dizziness/lightheadedness, post-nasal drip, nasal congestion, pressure at forehead or sinus, local hypothesia, left-side facial pain, numbness in throat, wheezy cough, and hot flashes. In general, subjects were able to tolerate the nasal CO_2 administrations, with approximately 90% of administrations being completed. The higher flow rate and direct flow nosepiece were not as well-tolerated as the lower flow rate and diffuse flow nosepieces.

3.3.4 Clinical Evaluations in Acute Migraine

To date, approximately 820 subjects with acute migraine have participated in clinical trials to evaluate the safety and preliminary efficacy of nasal CO_2 compared to a placebo control. Experience with nasal CO_2 to date support that nasal CO_2 can be administered safely at the doses planned for the current protocol. The data from these studies are summarized briefly below.

3.3.4.1 CH-2000-02 (Migraine Phase 1)

Study CH-2000-02 was a randomized (1:1), double-blind, placebo-controlled study conducted at three centers and examined the safety and efficacy of nasal CO_2 in the treatment of acute migraine. The CO_2 or nitrogen (control) was administered from hospital medical gas cylinders using disposable nosepieces. Subjects (n=54) self-selected a gas flow rate ranging from 0.20 L/min (3.3 mL/sec) to 0.69 L/min (11.4 mL/sec), depending on their own preference. Subjects were continuously monitored for pCO_2 levels, heart rate, electrocardiogram (ECG), respiratory rate, respiratory pattern, and blood pressure.

There were no SAEs reported in this study. Adverse events were mostly limited to application site irritation and included atypical sensations in the nasal cavity (discomfort, burning, stinging), watery eyes, throat discomfort, bad or unusual taste or smell, and dizziness/lightheadedness/ vertigo. Compared to pre-dose control, the study showed no clinically meaningful differences in the pCO_2 of subjects who received CO_2. There were no significant differences between CO_2 and placebo gases in any of the physiologic parameters measured at any time point.

The study provided preliminary evidence that nasal CO_2 is not systemically absorbed to any measurable degree and appears to be safe.

3.3.4.2 CH-2002-01 (Migraine Phase 2a)

Study CH-2002-01 was a randomized (1:1), double-blind, placebo-controlled, multi-center study and examined the safety and efficacy of nasal CO_2 in the treatment of acute migraine. The gas was delivered via hand-held dispenser (CAP-2, an earlier design of the current CO_2 drug delivery system) at a subject-selected flow rate of either approximately 0.3 L/min or approximately 0.9 L/min. Subjects were known International Headache Society (IHS)-defined migraineurs who were allowed to treat at any severity of pain at baseline (i.e., pain could be mild, moderate or severe), across multiple migraines.

There were no SAEs reported in this study. Adverse events most frequently reported included administration site reactions (irritation) and nausea.

The study demonstrated a 2-hour pain-free response of 36% in the CO_2 group (55 subjects) compared with 10% in placebo group (60 subjects), $p<0.01$, for the first attack. Relief was rapid with the majority of all responders in the CO_2 group reporting no pain at 30 minutes. Stratification according to pain at baseline showed a substantial improvement in the 2-hour pain-free response rate (52% CO_2, 10% placebo, $p<0.01$) for subjects with mild pain at baseline.

This study therefore provided preliminary evidence that nasal CO_2 is a potentially effective treatment for acute migraine.

3.3.4.3 CH-2004-03 (Migraine Phase 2b)

A randomized (2:1), double-blind, placebo-controlled, multi-center study examined the safety and efficacy of nasal CO_2 in the treatment of acute migraine. The gas was delivered via a hand-held dispenser (CAP-3, an earlier design of the current CO_2 drug delivery system) at flow rate of approximately 0.6 L/min. Subjects were known IHS-defined migraineurs treating a typical migraine at moderate or severe pain.

There were no SAEs reported. The most common AEs were administration site irritation (i.e., stinging, burning, numbness, tingling).

The study showed a 2-hour pain-free response of 23% for CO_2 (89 subjects) versus 4% for placebo (45 subjects), $p<0.01$. The trial included a pulsed dosing arm where the efficacy comparison to placebo was not statistically significant.

The trial provided further evidence that nasal CO_2 may be an effective treatment for acute migraine. Statistically significant efficacy was observed at 2 hours with rapid onset of effect and the effect was sustained at 24 hours.

3.3.4.4 C112 (Mild Headache Study)

Study C112 was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of nasal CO_2 in the treatment of mild headache in migraineurs. This was an adaptively designed study that used a two-step randomization process. First, eligible subjects were assigned to either active or placebo. Then, upon experiencing a qualifying headache, subjects would call into the Interactive Voice Response System (IVRS) to receive their dosing regimen assignment.

Two-hundred ninety-two subjects were randomized into Study C112 and 244 completed the study. Of the 244 subjects, 102 subjects (69 active and 33 placebo) dosed 10 sec/nostril 1 time, 49 subjects (29 active and 20 placebo) dosed 20 sec/nostril 1 time, 21 subjects (15 active and 6 placebo) dosed 40 sec/nostril 1 time, 42 subjects (31 active and 11 placebo) dosed 10 sec/nostril 4 times, and 30 subjects (21 active and 9 placebo) dosed 20 sec/nostril 4 times.

The safety profile of nasal CO_2 was similar to what has been seen in prior studies with the most common adverse events being nasal discomfort and lacrimation. There were no serious adverse events in subjects who treated a headache with the study drug and no discontinuations due to adverse events.

The study showed that lower doses appear to be efficacious, and higher doses do not seem to add to efficacy. The 10 sec/nostril 1 time dose group was the most efficacious in this study (showing a 38.5% pain-free at 2 hours versus 25.8% for placebo), with the 10 sec/nostril 4 times showed similar efficacy (showing a 36.7% pain-free at 2 hours versus 18.2% for placebo). None of the groups achieved statistical significance against corresponding placebo, but the 10 sec/nostril 1 time dose group showed strong statistical trends towards efficacy (Bayes p=0.09). The study was primarily designed to select the appropriate dose for future studies, and determined that dose to be 10 sec/nostril which can be repeated up to 4 times.

3.3.4.5 C113 (Phase 3, Moderate to Severe Migraine Study)

Study C113 was a multi-center, double-blind, placebo-controlled, parallel group trial that evaluated the safety and efficacy of nasal, non-inhaled administration of CO_2 in the treatment of moderate to severe migraine.

Subjects were allowed to treat up to a total of 4 moderate to severe migraines within a 56-day treatment period. Headaches treated with the study drug (nasal CO_2 or placebo) were to be at least 48 hours apart.

Each dose consisted of an administration of 10 sec/nostril. If subjects still had pain and/or any other symptoms after the initial dose then they were permitted to take a dose after completing the symptom assessment at 15, 30, and/or 60 minutes after the initial dose. Thus, subjects could

have taken up to 4 doses of study drug to treat a headache. Subjects with an ongoing headache at 2 hours were permitted to take rescue medication.

A total of 35 subjects were enrolled in this study. This study was performed in collaboration with the Navy's Advanced Medical Development Program and medicated through the Omnibus program. Due to a low enrollment rate and limited funding available to conduct this study, this study was closed prior to meeting the enrollment goal of 450 subjects.

The analysis of all subjects treated (CO_2 = 17; Placebo = 13) did not show statistical significance in any of the four co-primary endpoints (pain free, nausea/vomiting free, photophobia free, or phonophobia free) at two hours after the initiation of treatment.

The safety profile of nasal CO_2 was similar to what has been seen in prior studies. The most common adverse event reported was nasal discomfort (CO_2 = 36.8%, placebo = 12.5%). All reported events typically resolved with cessation of administration. There were one SAE; it was due to a bicycle accident and unrelated to the study drug.

The most reported AEs were mild or moderate in severity. Of the 15 severe AEs reported, only 4 (nausea [n=1], nasal discomfort [n=2], and migraine [n=1]) were deemed related to study drug or study device; however, all 4 of these AE resolved with the cessation of application of the study drug/device. There were 2 discontinuations due to AEs. One was due to severe nausea and identified as being probably related to study drug; however, this subject was assigned to placebo. The other was due to neck pain and deemed unrelated to study drug and/or study device; the subject withdrew from the study because non-allowed medication was required for the treatment of the neck pain.

3.3.5 Clinical Evaluations in Allergic Rhinitis

To date, approximately 975 subjects with allergic rhinitis have participated in clinical trials to evaluate the safety and preliminary efficacy of single doses of nasal CO_2 compared to a placebo control. In addition, a study was conducted to assess the consumer experience of CO_2 nasal spray in subjects with nasal congestion. One-hundred forty-seven subjects participated in that study. The doses administered in the allergic rhinitis studies have been smaller than those used for migraine, with the highest being approximately 1.2 L. The data from these studies are summarized briefly below.

3.3.5.1 SAR-2005 (Seasonal Allergic Rhinitis Single-Dose Study)

Study SAR-2005 was a double-blind, placebo-controlled, in-clinic, single-center study conducted to evaluate the safety and efficacy of a single dose of nasal CO_2 on the symptoms of seasonal allergic rhinitis (SAR).[9] Eighty-nine subjects were treated with 60 seconds per nostril of either CO_2 (60 subjects) or placebo (29 subjects). The study tested one CO_2 dose of approximately 1.2 L (60 sec/nostril, approximately 0.6 L/nostril) versus placebo (air). There were no serious

adverse events (SAEs) reported. Nasal stinging or burning and watery eyes were the most common adverse events observed in this study.

In this study, a single dose (two 60-second nasal CO_2 administrations) resulted in rapid (10 minutes) and sustained (≥ 4 hours) relief of nasal symptoms (i.e., rhinorrhea, nasal congestion, nasal itching, and sneezing) compared to placebo.

3.3.5.2 C211 (Perennial Allergic Rhinitis Single-Dose Study)

Study C211 was a randomized (2:1), double-blind, placebo-controlled, in-clinic, multi-center study and examined the safety and efficacy of nasal CO_2 on the symptoms of perennial allergic rhinitis (PAR). The study tested two dose durations (10 and 30 sec/nostril) and two flow rates (0.3 and 0.6 L/min) for CO_2 versus placebo (no gas).[1] The primary endpoint was mean change from baseline in total nasal symptom score (TNSS, the sum of the scores of rhinorrhea, average score the right and left nostril congestion, nasal itching, and sneezing) at 30 minutes, separately comparing the 10 and 30 sec/nostril dosing groups. A total of 348 subjects (previously diagnosed with PAR) were randomized and treated.

There were no SAEs reported in this study. The treatment was generally well-tolerated and the most frequent AEs reported were nasal discomfort, lacrimation increased, headache, rhinalgia, rhinorrhea, and throat irritation.

The study provided further evidence that nasal CO_2 may be a safe and effective treatment for both the nasal and non-nasal symptoms (i.e., lacrimation, eye redness, ear/throat itching, eye itching) of PAR. It had a rapid onset of effect that was sustained for several hours compared to placebo.

3.3.5.3 C213 (Perennial Allergic Rhinitis Multi-Dose Study)

Study C213 was a randomized, double-blind, placebo-controlled, single-center, cross-over study to evaluate the effect of nasal, non-inhaled CO_2 on nasal congestion using acoustic rhinometry in subjects with PAR. Twenty (20) subjects were randomized to receive study drug in one of four treatment sequences. Each sequence consisted of the same four treatments in different order. These four treatments were:

Dose A: Nasal CO_2 (0.5 SLPM) for 5 sec/nostril
Dose B: Nasal CO_2 (0.5 SLPM) for 10 sec/nostril
Dose C: Nasal CO_2 (0.5 SLPM) for 30 sec/nostril
Dose D: Placebo (0.0 SLPM, no gas) for 30 sec/nostril

All 20 subjects completed all four treatments and completed the study.

CO_2 was delivered via a nosepiece that was attached to a CO_2 cylinder by plastic tubing. The flow rate was controlled by a flow control valve at 0.0 SLPM for the placebo dose for (Dose D) and 0.5 (± 0.05) SLPM for the active doses (Doses A, B, and C).

No consistent changes in nasal congestion were seen as measured by acoustic rhinometry.

3.3.5.4 C215 (Seasonal Allergic Rhinitis Multi-Dose Study)

Study C215 was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of nasal CO_2 administered twice daily for 14 days in the treatment of seasonal allergic rhinitis. Four-hundred fifty-three (453) subjects met the randomization criterion of a minimum average score of 6 on the total nasal-symptom score (TNSS, a 0 - 3 scale to evaluate the severity of congestion, runny nose, itchy nose, and sneezing) and were randomized, 229 to the CO_2 treatment and 224 to the placebo treatment. Of the subjects randomized, 451 (99.6%) had at least one administration of the study drug and 447 (98.7%) completed the study.

CO_2 and placebo (no gas) were administered via hand-held dispensers. Subjects completed symptom diaries every morning and evening over the 14-day treatment period.

The baseline characteristics were similar between the two groups with respect to age, sex, ethnicity, and race. The reflective Total Nasal Symptom Score (TNSS) at baseline was 9.6 ± 1.7 in the CO_2 group and 9.3 ± 1.7 in the placebo group.

An analysis of treatment effects over the entire 14-day treatment period noted that the change from baseline in reflective total nasal symptom scores for treatment compared to control subjects were 2.0 and 1.7, respectively (p=0.1440).

While the primary analysis of efficacy for the 14-day treatment did not show a significant benefit, statistically significant changes from baseline in TNSS were seen after the first dose on Day 0. The changes from baseline in instantaneous TNSS for treatment compared to control subjects at 30 minutes were -2.4 and -1.6, respectively (p=0.0001), and at 6 hours were -2.2 and -1.5, respectively (p=0.0139).

3.3.5.5 C216 (Phase 2, Seasonal Allergic Rhinitis)

Study C216 was a randomized (2:1), double-blind, placebo-controlled, multi-center, parallel group, pilot study to evaluate the efficacy and safety of nasal, non-inhaled carbon dioxide used as-needed, up to 6 times per day, for 14 days in subjects with SAR. Thirty-two (32) subjects who completed at least 2 SAR episode diaries per day and had a TNSS of 8 out of a maximum of 12 for at least 2 of the SAR episodes during the 3 days prior to randomization were randomized, 19 to the CO_2 treatment and 13 to the placebo treatment. All 32 subjects completed the study.

Carbon dioxide and placebo (no gas) were administered via hand-held dispensers. Subjects completed instantaneous symptom diaries immediately prior to dosing (pre-dose assessment), 30 minutes after dosing (post-dose assessment) as well as reflective diaries in the mornings and evenings during the 14-day treatment period.

The baseline characteristics were similar between the two groups with respect to age, sex, ethnicity, and race. Subjects in both groups dosed an average of 3 times per day. Analysis of all treated episodes (CO_2=816, placebo=516) showed a statistically significant beneficial change in pre-dose TNSS and 30-minute post dose TNSS for CO_2 (-2.00) versus placebo (-1.49), effect size=-0.51, $p<0.0001$.

3.3.5.6 C218 (Phase 2, Seasonal Allergic Rhinitis)

Study C218 was a randomized (2:1), double-blind, placebo-controlled, multi-center, parallel group, pilot study to evaluate the efficacy and safety of nasal, non-inhaled carbon dioxide administered four times per day, for 14 days in subjects with SAR. Thirty-three (33) subjects met the randomization criterion of a minimum average reflective TNSS of 8 out of a maximum of 12 and were randomized, 22 to the CO_2 treatment group and 11 to the placebo group. All 33 subjects completed the study.

Carbon dioxide and placebo (no gas) were administered via handheld dispensers. Subjects completed instantaneous symptom diaries immediately prior to dosing (pre-dose assessment), 30 minutes after dosing (post-dose assessment) as well as reflective diaries in the mornings and evenings during the 14-day treatment period.

The baseline characteristics were similar between the two groups with respect to age, sex, ethnicity, and race. Analysis of all treated episodes (CO_2=1220, placebo=602) did not show a statistically significant beneficial change in pre-dose TNSS and 30-minute post-dose TNSS for CO_2 (-0.78) versus placebo (-0.65), effect size=-0.13, $p<0.6302$.

3.3.5.7 RH01910 (Phase 2, Nasal Congestion)

Study RH01910 was a multi-center, monadic, open-label two-part repeat-dose, consumer experience study in subjects with nasal congestion. In the first part of the study, recruited subjects were provided a description of a new treatment option. Interested subjects were offered the opportunity to enter the clinical study. Eligible subjects received one dose, 10 sec/nostril of nasal CO_2 in the study clinic under medical supervision. Afterward, subjects who wished to continue in the study were allowed to take the nasal CO_2 product home for an additional six days of use, 10 sec/nostril up to 4 times daily. Subjects used a diary to record the number of times the product was used and their nasal congestion symptoms before and after use.

This study showed that nasal CO_2 was perceived well in subjects with nasal congestion.

The nasal CO_2 was tolerated well in this study. Adverse events were mild and consistent with previous studies. No serious or unexpected adverse events were reported.

3.3.6 Clinical Evaluation in Temporomandibular Disorders

Study C301 was a randomized, placebo-controlled study to evaluate the safety and efficacy of nasal, non-inhaled administration of CO_2 in subjects with pain and other symptoms related to temporomandibular disorders (TMD). One-hundred (100) subjects were randomized and treated with CO_2 or placebo in a 2:1 randomization respectively. For both treatment groups, a single dose consisted of 2 sequential administrations which were to last for 30 seconds in each nostril (60 sec/dose). Subjects in the CO_2 group received up to 3.6 L of CO_2; subjects in the placebo group received up to 3.6 L of Air. The data from this study are summarized in the current Investigator's Brochure for Carbon Dioxide Drug Delivery System.

3.4 Risk/Benefits

The adverse events anticipated with nasal CO_2 include: administration site reactions (such as nasal passage irritation, tingling, burning, pain, rhinorrhea, congestion, etc.), increased lacrimation, nausea, headache, throat irritation, dysgeusia, dizziness, pharyngolaryngeal pain, epistaxis, parosmia, post-nasal drip, rhinalgia, rhinorrhea, migraine headache, upper respiratory tract infection and feeling cold. There is minimal risk of systemic effects of CO_2 as relatively small volumes are administered locally to the nasal cavity. Even if the product were inadvertently inhaled, the amount of CO_2 is minimal compared to the minute volume of respiration.

3.5 Dose Rationale

The trial is designed to evaluate a dose of nasal CO_2 at 10 sec/nostril administered up to 6 times for one attack in a cluster period.

The dose selected for evaluation in this study are based on safety data from the Phase 2 single-dose studies in SAR and PAR, the multi-dose study in SAR, as well as from three studies in patients with migraine, and a study in healthy volunteers as described in Sections 3.3.3, Section 3.3.4, and Section 3.3.5, respectively. Prior migraine studies evaluated a wide range of doses (from 10 sec/nostril 1 time [0.17 L] to 20 sec/nostril 4 times [1.67 L]). Single doses evaluated in allergic rhinitis (AR) studies have ranged from 0.1 L to 1.2 L of CO_2. In a SAR study, subjects were allowed to administer up to 1.0 L of CO_2 per day for two-weeks. Thus, the dose selected for evaluation in this study is within the range of doses used in previous studies. In these previous studies, nasal CO_2 was found to be safe.

3.6 Trial Conduct

This trial will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), Good Clinical Practice (GCP), and applicable regulatory requirements and standards. No amendment to the protocol or deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

3.7 Population

The trial population will include men and women ages 18 years old and above who have an established diagnosis of cluster headache, as defined by International Classification of Headache Disorders (ICHD), third edition, beta version guidelines (ICHD-3 beta, Cephalalgia 2013.[3]

4.0 TRIAL OBJECTIVES

4.1 Primary Objective

The primary objective of this trial is to evaluate the safety and efficacy of nasal CO_2 for the treatment of cluster headache.

4.2 Secondary Objectives

Key secondary objectives are to determine the effect of nasal CO_2 in the treatment of cluster headache:

- freedom from pain at 5-60 minutes
- headache relief at 5-60 minutes
- rescue medication usage
- subject satisfaction

5.0 TRIAL DESIGN

This is an open-label, investigator-sponsored, pilot study. Subjects agreeing to participate in the study and meeting the eligibility criteria assessed at the screening visit will be enrolled in the study. The length of time between screening and treatment will last between 0 days to a maximum of 12 weeks. Subjects who enter the screening phase during a cluster headache episode and meet the study eligibility criteria can immediately enter the treatment phase and may opt to treat their cluster headache episode in the clinic. Subjects who are not in a cluster

headache episode, who meet initial screening eligibility criteria, can remain in the screening phase for up to 12 weeks until their next cluster episode begins. Upon initiation of a cluster headache episode, subjects will enter the treatment period.

Subjects will be trained and demonstrate the proper use of the hand-held dispenser containing CO_2 calibrated to deliver 0.5 standard liters per minute (SLPM). This dispenser will be provided to subjects for use in the clinic or home. Subjects will be instructed to use the nasal CO_2 dispenser, 10 sec/nostril, as needed up to 6 times to treat one attack. Each dose must be separated by 3-5 minutes. Subjects should treat only one attack in a 24-hour period. Subjects may treat up to three cluster headache attacks during the treatment phase of this study. One hour after the first dose subjects can choose to treat with investigator-approved rescue medication. Subjects will be asked to complete an online diary after the completion of the dosing. Diary assessments will collect pain severity (0=none, 1=mild, 2=moderate, 3=severe), symptoms (such as tearing, nasal congestion, and running nose), nasal CO_2 usage, acute medication usage, satisfaction of treatment, number of cluster attacks, and unusual symptoms. Subjects will be contacted by phone within 3 days of the first use of the nasal CO_2 dispenser to assess adverse events (AEs) and medication usage. A total of 25 subjects will enter the treatment period and be instructed to treat up to three cluster headaches with nasal CO_2. Within 7 days of treating their last cluster headache episode, subjects will return for an end of study visit.

5.1 Primary, Secondary, and Exploratory Endpoints

5.1.1 Primary Endpoint

Greatest change from pre-treatment headache pain intensity to post treatment at any time point within 30 minutes of Nasal CO_2 administration.

5.1.2 Secondary Endpoints

- Percentage of subjects experiencing headache pain freedom at 5-60 minutes within the treated attack
- Percentage of subjects with headache relief at 5-60 minutes within the treated attack
- Rescue medication usage
- Subject satisfaction
- Cluster recurrence

Exploratory endpoints include but not limited to:

- Number of doses per treated attack
- Consistency of response with repeated treated attacks

All primary, secondary, and exploratory efficacy endpoints will be analyzed for the all headaches analyses as well.

5.2 Study Treatment

5.2.1 Dose Description

This is an open-label study so all eligible subjects will receive a nasal CO_2 hand-held dispenser. One dose will consist of a 10 second administration of nasal CO_2 to each nostril. Subjects will be instructed to use the nasal CO_2 dispenser, 10 sec/nostril, as needed up to 6 times to treat one attack. Each dose must be separated by 3-5 minutes. Subjects should treat only one attack during a 24-hour period with the investigational product. Subjects may treat up to three cluster headache attacks during the treatment phase of this study.

Subjects may receive up to a total of 1.0 L of CO_2 if they treat one attack with 6 doses. Subjects may receive a total of 3.0 L of CO_2 if they treat three headache attacks with 6 doses of CO_2 during this study.

5.2.1.1 Nasal CO_2 Dispensers

The dispensers are calibrated to deliver CO_2 at a target flow rate of 0.5 standard liters per minute (SLPM).

5.2.2 Packaging and Labeling

Treatment kits will consist of one (1) dispenser and the Directions for Use. The directions will specify that the dispensers cannot be taken aboard an airplane. There will be replacement dispensers available in the event subjects damage or misplace their dispensers. When subjects are enrolled, they will be assigned a unique subject identification number and a unique kit number.

Once eligibility is confirmed, the study site personnel will review the Directions for Use with the subjects and will give the copy of the Directions for Use to the subjects to take with them.

5.2.3 Storage and Handling

The dispenser should be stored at room temperature (59 – 86 °F / 15 – 30 °C). Prolonged exposure to temperatures above or below ambient conditions should be avoided.

The contents of the dispenser are under pressure. Therefore, exposure of the dispenser to temperatures ≥ 120 °F (50 °C), puncture, or other damage to the dispenser may cause injury and/or loss of contents.

At this time, the Transportation Security Administration (TSA) does not allow the dispenser to be carried aboard any commercial aircraft. If the dispenser is carried through TSA security or onto any commercial flight, it will be confiscated.

Neither the dispenser nor its packaging is child-resistant. It has not been tested in children for safety. Therefore, the dispenser should be kept out of the reach of children.

The dispenser is an investigational drug product and must be stored, handled, and administered in accordance with this protocol, the Investigator's Brochure and labeling, as well as all applicable laws, regulations, and institution requirements.

5.3 Duration

Once enrolled, each subject's participation in the trial may last up to 84 days (12 weeks) or once the subject treats up to 3 cluster headache attacks with the nasal CO_2 dispenser, whichever occurs first. There will be two scheduled clinic visits, Screening and End of Study Visit. The subject may return to the clinic 4 weeks and 8 weeks after the screening visit as necessary for a replacement dispenser. The End of Study Visit should occur within 7 days after the subject treats his/her last cluster headache attack or within 7 days after the completion of the 84-day treatment period, whichever occurs first. If a subject has not treated any cluster headaches during the 12 weeks treatment phase they can be allowed to continue in the study for an additional 12 weeks at the discretion of the Investigator.

5.4 Discontinuation

Based on trials conducted with nasal CO_2 to date, it is not expected that serious safety issues will arise that would require a discontinuation of the study. If such issues do arise, the sponsor, Dr. Cady, will, in consultation with the Capnia, appropriate regulatory authority(ies), and/or IRB, take the steps necessary to modify or discontinue the trial.

Since this is an open-label, pilot study, there will be an ongoing review of the data. The trial may also be discontinued or modified in the event that the study treatment is not showing any signs of efficacy.

The criteria for the discontinuation of the participation of individual subjects are explained in Section 6.3.

5.5 Investigational Product Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain an inventory record to document the receipt and dispensation of each nasal CO_2 dispenser. All used and unused investigational product will be returned to Capnia or designee. Investigational product will not be dispensed to any person who is not a qualified study subject under this protocol. The investigational product will be dispensed only by study site personnel designated by the Investigator in writing on the Study Site Personnel Signature Log. The investigational product must be dispensed only within and from the institution listed in the study contract and Form FDA 1572. The maintenance of study-related investigational product accountability records does not preclude the Investigator's responsibilities to maintain additional records in accordance with all national and/or local institutional requirements for investigational medication.

Subjects are required to return the used and/or unused dispensers to the study site at the End of Study Visit. Upon completion or termination of the study or on request, all used and unused investigational product will be accounted for and returned to Capnia or designee.

5.6 Data Identification

Clinical data will be directly entered into the combined eSource/CRF forms by members of the study site personnel. Site personnel will be responsible for instructing subjects on the requirement for timely and daily completion of the electronic diary (eDiary). Subject-reported adverse events and concomitant medications collected during the out-subject treatment period will be recorded by the subject in the eDiary. This diary will be reviewed by the Investigator and/or the appropriate study site personnel, applicable information will be collected, recorded into the subject's eSource/eCRF. The electronic diaries will be automatically collected after the completion of each diary and stored with the subject's eSource/CRF documents. Subjects will record their headache-related symptom assessments as well as the details regarding the nasal CO_2 administration in an electronic diary.

6.0 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be considered eligible for study entry:

- Male or female, 18 years of age and older.
- History of cluster headache, as defined by International Classification of Headache Disorders (ICHD), third edition, beta version guidelines (ICHD-3 beta, Cephalalgia 2013).
- Stable on concomitant medications, excluding those for the treatment of cluster headache, for at least 60 days prior to enrollment.

  Note: Subjects are allowed to use their usual standard of care for the preventative treatment for their cluster headache. Acute/abortive medications maybe used 60 or more minutes after the initial dose, limited to the following: triptans; high-flow oxygen.

- If female and of childbearing potential, have a negative urine pregnancy test at the time of Screening.
    - To not be considered childbearing potential a subject must be surgically sterile, have had a hysterectomy or tubal ligation, post-menopausal for at least 1 year, or otherwise incapable of pregnancy.
- Capable of completing online headache diary with access to internet.
- Able to provide written Informed Consent.

6.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria to be considered eligible for study entry:

- Recent nasal/midface trauma (< 3 months).
- Recent nasal/sinus surgery (< 3 months).
- Severe respiratory distress in the last 6 months.
- Neoplasm such as Angiofibroma, sinus tumor, granuloma.

- Nasal congestion present more than 10 days with fever (temperature ≥ 100.4 °F) and nasal mucous is an abnormal color.
- Surgery to treat cluster headache.
- History of aneurysm, intracranial hemorrhage, brain tumors or significant head trauma.
- Structural intracranial or cervical vascular lesions that may potentially cause headache attacks.
- Other significant pain problem (including cancer pain, fibromyalgia and trigeminal neuralgia) which in the opinion of the clinician, may interfere with the study.
- Psychiatric disorder which in the opinion of the Investigator may interfere with the study.
- Pregnant, actively trying to become pregnant, or breastfeeding, and/or is unwilling to use an accepted form of birth control.
    - Acceptable forms include: complete abstinence from intercourse from 2 weeks prior to administration of study drug, throughout the study, and for 7 days after completion or premature discontinuation from the study; sterilization of male partner when in a monogamous relationship; intrauterine device or implant with published data showing lowest expected failure rate is less than 1% per year; double barrier method (i.e., 2 physical barriers OR 1 physical barrier plus spermicide) for a least 1 month prior to Screening Visit and throughout study; or hormonal contraceptives for at least 3 months prior to Screening Visit and throughout study.
- Skin around and inside the nasal passage that is dry, cracked, oozing, or bleeding.
- Recurrent nose bleeds which in the opinion of the Investigator, may interfere with the study.
- Is participating in any other therapeutic clinical investigation or has participated in a clinical trial and received treatment in the preceding 30 days

6.3 Subject Withdrawal

Subjects are free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. Justifiable reasons for the removal of a subject from the study include but are not limited to:

- The subject's request
- The subject is non-compliant in the opinion of the Investigator
- The subject resumes or initiates other medication not permitted in this study
- The subject experiences an adverse event which, regardless of seriousness or severity, prohibits further participation in the study
- The subject does not have a cluster headache episode within 84 days (12 weeks) after Enrollment
- The subject becomes pregnant, at which time she is to inform the study site personnel

Enrolled subjects who withdraw from the study must return to the study site for the End of Study Visit. If during this visit, the Investigator determines that the subject has an ongoing study drug-related or study device-related adverse event, the subject will be followed until resolution or stabilization.

The reasons for withdrawal must be documented accordingly in the subject's eSource documents/eCRF. Subjects who withdraw early from the study may be replaced.

6.4 Screen Failures

Subjects who do not meet the eligibility criteria at the Screening Visit will be considered screen failures. These subjects will be instructed by the study site, if the Investigator is the subject's doctor, how to manage their cluster headaches (i.e., continue to use the medication they were previously taking for their cluster headaches prior to being screened for this study) or be referred to their regular physician for management of their cluster headaches. These subjects will not be required to undergo the End of Study Visit procedures.

7.0 TREATMENT OF SUBJECTS

Below is a brief description of the treatments to be administered in this study. Please refer to Section 5.5 Trial Treatment and the Investigator's Brochure for more information regarding nasal CO_2.

7.1 Treatments to be Administered

7.1.1 Nasal CO_2 Dispenser

The subject will administer the nasal CO_2 to one nostril and then to the second nostril (i.e., 10 seconds to the right nostril then 10 seconds to the left nostril). The administrations should

occur in succession and there should be no more than one (1) minute delay between administration each nostril. One dose consists of a 10-second administration of CO_2 to each nostril. If subjects still have pain and/or any other symptoms after the initial dose then they may take up to 5 doses after the initial dose. Each dose must be separated by 3-5 minutes. Thus, subjects may take up to 6 doses of study drug to treat an attack.

If the subject is feeling congested at the time of the study drug administration, he/she may blow his/her nose prior to each dose. The subject will be informed to hold his/her breath or to breathe in and out of his/her mouth during the administration, whichever is more comfortable to the individual subject.

Subjects will treat up to 3 cluster headache attacks within a 84-day period (12 weeks) of their Screening Visit (i.e., when they were enrolled into the study). Subjects will return to the clinic 4 weeks and 8 weeks after the Screening Visit for a replacement dispenser, as necessary.

7.2 Medication

7.2.1 Concomitant Medication

Concomitant medications required by subjects must be documented on their eSource/CRF documents. Patients must be stable on concomitant medications, excluding those for the treatment of cluster headache, for at least 60 days prior to enrollment

Subjects are allowed to take their prescription migraine and cluster prophylaxis medication.

7.2.2 Medications Not Permitted

The investigator or designee will instruct the subjects **NOT** to treat a cluster headache with the study drug if, within 12 hours prior to the onset of the attack, they used any of the following:

- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Non-prescription analgesics
- Narcotic analgesics
- Triptans
- Ergotamine medication or derivatives

- Any other medications or treatments for headache (e.g., homeopathy, natural health products, acupuncture, etc.)

7.2.3 Rescue Medication

Subjects will be allowed to take rescue medication as prescribed by their physician if the headache(s) does/do not resolve or worsen(s) after completing the one-hour assessment. Subjects who take rescue medication will be asked to record the details of all medication taken through the 24-hour assessment (e.g., what medication they took, dose, when they took it, etc.) in the eDiary. The data recorded by the subjects in the diaries will be discussed at the End of Study Visit and all rescue medication taken by the subjects will be recorded on the subjects' appropriate eSource/eCRFs. If a subject uses rescue mediation they are not allowed to treat the same headache again with Investigational Product.

Subjects who take rescue medication shall record the severity of their headache and associated symptoms at the 1 hour assessment.

7.3 Monitoring for Subject Compliance

Subjects return to the site approximately 4 weeks after enrollment to exchange study drug and determine the subjects' compliance with nasal CO_2 administration and eDiary completion. If necessary, at these visits subjects can receive re-training if it is determined there are issues with study drug administration and/or diary completion.

8.0 STUDY PROCEDURES

The following sections describe the procedures and assessments that will be performed during the study. The Schedule of Events, located in Section 8.2, indicates the frequency of these procedures and assessments.

8.1 Description of Study Procedures and Assessments

8.1.1 Informed Consent

At the beginning of the Screening Visit, potential participants will be given an IRB-approved informed consent form by a member of the study site personnel (i.e., study coordinator, Investigator, or other study site personnel). Potential participants will be provided time to read the consent form as well as the opportunity to ask questions and have their questions answered prior to the initiation of any study-specific assessments. Subjects must voluntarily provide written informed consent before any study-related assessments are performed. Once signed by the subject and the study site personnel performing the consent process, a copy of the consent form will be given to the subject and the original will be stored in the study site's files. The

subject's medical records/source documents must include documentation that written informed consent was obtained from the subject, and that the subject received copies of the signed, fully-executed informed consent form.

8.1.2 Medical History, Medications and Demographics

Subjects will be asked about their medical history and any medication and supplements they are currently taking or have taken within 30 days of the Screening Visit. Subjects will also be asked about their cluster headache history (e.g., age of diagnosis, typical associated symptoms, cluster headache pattern, etc.) and the pharmacotherapy and/or alternative treatment (e.g., homeopathy, natural health products, etc.) they have taken for their cluster headaches. In addition, the subject's demographic information (age, gender, race, and ethnicity) will be collected.

8.1.3 Physical Examination

A full physical exam, including all major body systems and neurological exam, will be performed at the Screening Visit and at the End of Study Visit. Any conditions or symptoms reported after the subject is enrolled will be recorded as an AE on the AE eCRF. This includes new events after nasal CO_2 administration, conditions that become more severe or increase in frequency, any disease-related signs or symptoms present at the Screening Visit (see Section 8.1.2) that have worsened in severity or frequency, as well as any event or finding that the Investigator feels is clinically significant.

8.1.4 Vital Signs

Vital signs include temperature, systolic and diastolic blood pressure, and pulse rate will be measured at the Screening Visit and at the End of Study Visit. Unscheduled vital signs may be measured as clinically necessary and shall be reported in the subject's eSource/eCRF form. Height and body weight will be measured at the Screening Visit only.

8.1.5 Nasal Mucosal Examination

A nasal mucosal examination will be performed at the Screening Visit and at the End of Study Visit to determine presence of polyps, nasal passage redness, deviated septum, purulence or other abnormalities. Subjects with the presence of any of these that are considered clinically significant prior to enrollment at the Screening Visit will be excluded from participation in the study. The results of the examination shall be reported in the subject's eSource/eCRF. Clinically significant changes that are noted at the End of Study Visit and/or during an unscheduled nasal mucosal examination will be recorded as an AE on the AE eCRF. If significant abnormalities are found, then the subject may be referred to an ear, nose and throat specialist.

8.1.6 Urine Pregnancy Test

Female subjects of childbearing potential will be given a urine pregnancy test at the Screening Visit and at the End of Study Visit. Subjects with a positive urine pregnancy test will be excluded or withdrawn from the study.

8.1.7 Enrollment

Subjects who sign the informed consent form, complete all screening evaluations, and meet the eligibility criteria outlined in Sections 6.1 and 6.2 will be eligible for enrollment into the study.

8.1.8 Training

A member of the study site personnel, the trainer, will train enrolled subjects on the following:

- How to complete the headache-related symptom assessments and enter the nasal CO_2 administration details in eDiaries
- How and when to administer the nasal CO_2 using the Directions for Use as a guide
  - This includes using the activated device one time 5 seconds/nostril
- How to enter data (e.g., to medical problems, medications/treatments, etc.) in the eDiary
- When it is acceptable to take rescue medication, if needed
- When the dispenser is operating properly (i.e., makes a hissing sound, which will be demonstrated by the trainer during the Screening Visit) and to contact the site if the dispenser is not operating properly
- Contact site if experiencing any significant AEs and, if after hours, subject should go to the emergency room

It is the responsibility of the study site personnel to ensure that each subject completely understands how to do all of these tasks. This training should be documented in the subject's eSource/eCRF documents.

8.1.9 Subject Diary and Assessments

The primary and most of the secondary endpoint data will be collected from the electronic daily headache diary. Site personnel will be responsible for instructing subjects on the requirement for timely completion of the electronic diary. An email will be sent to subjects for completion of their headache diary containing a link to the diary. This link will take them to a survey queue

where all diaries will be available for completion. The diary for each headache should be completed during or immediately after each headache treated with nasal CO_2 and will document:

- Pain severity: (0=none, 1=mild, 2=moderate, 3=severe)
- Baseline pain severity
- Study medication usage
- Rescue medication usage
- Pain severity after initial treatment with nasal CO_2, symptoms at 5, 15, 30, and 60 minutes following treatment
- Headache resolution
- Unusual symptoms

All assessments must be completed as close as possible to the protocol-specified time of the assessment.

8.1.10 Treatment of Cluster Headaches

Subjects will be allowed to treat up to 3 cluster attacks during this study.

If subjects still have pain and/or any other symptoms after the initial dose then they may take up to 5 more doses (each dose must be separated by 3-5 minutes). Thus, subjects may take up to 6 doses of nasal CO_2 to treat a headache.

Subjects will record the details about each dose taken (i.e., time of nasal CO_2 administration, duration of administration) in the eDiary.

8.1.11 Adverse Events

Subjects will be monitored for safety from the time they are enrolled until the End of Study Visit.

Non-serious adverse events (NSAEs) will be collected beginning after the first dose of study medication through the End of Study Visit and will include any change from the subject's condition at Screening.

SAEs will be collected following enrollment and will include any change from the subject's baseline condition at Screening. SAE collection will conclude at End of Study or until resolution of the SAE if it extends beyond the End of Study Visit.

Subjects will be instructed to record in the eDiary any adverse events they experience from the time they are enrolled at the Screening Visit until their End of Study Visit. Any conditions or symptoms reported will be recorded as an AE in the subject's AE eCRF page. Subjects who have an ongoing AE related to study drug and/or study device will be followed until resolution or stabilization of the event.

At the End of Study Visit, subjects will be asked by the Investigator or an appropriate member of the study site personnel about any AEs they have experienced since the previous visit. All AEs recorded by the subject in the eDiary will be discussed and reviewed by the Investigator or an appropriate member of the study site personnel, recorded in the subject's source documents, and on the appropriate eCRF. Subjects will be instructed to contact the study site in the event they experience any significant AEs. At the discretion of the Investigator, the subject may be asked to come to the study site for an Unscheduled Visit. Additional information regarding AEs is provided in Section 9.0.

8.1.12 Concomitant Medications / Procedures

Medications taken and procedures performed, within 30 days prior to the Screening Visit will be recorded in the subject's eSource/eCRF. Medications taken after the Screening Visit and until the end of the subject's participation in the study (End of Study Visit) will be recorded by the subject in the eDiary. Any rescue medication taken will also be recorded in the subject's eDiary. At the End of Study Visit as well as at any unscheduled visits, subjects will be asked about the medications, procedures and/or alternative treatments (e.g., homeopathy, natural health products, etc.) they have taken since their previous visit. All medication and procedures including rescue medication recorded by the subject on the diary will be discussed and reviewed by the Investigator or an appropriate member of the study site personnel, recorded in the subject's eSource/eCRF.

8.1.13 Telephone Contact

Subjects will be contacted within 3 days of treating their first headache attack with nasal CO_2 to answer any questions the subject may have, to assess if there are any problems with compliance, or any concerning AEs. Furthermore, during the treatment period, approximately at 4 and 8 weeks after the Screening Visit, a member of the study site personnel will follow-up with the subject via telephone to answer any questions the subject may have, to assess if there are any problems with compliance or any concerning AEs and, as necessary, to request that the subject return to the clinic for a replacement dispenser.

If it is determined that the subject is non-compliant with the requirements of this study, then it is the Investigator's discretion whether or not to withdraw the subject from the study.

8.2 Schedule of Events

Study Procedures	Screening	Treatment	End of Study Visit[1]
Informed Consent	X		
Eligibility	X		
Medical History/ Medications / Demographics	X		
Physical Examination including Neurological and Nasal Mucosal Exam	X		X
Vital Signs	X		X
Urine Pregnancy Test	X		X
Subject Training	X		
Subject eDiary, AE/ConMed diary, and Questionnaire Instruction	X		
Investigational Product Dispensation	X	X[2]	
Accountability of Investigational Product Study Drug and Study Supplies	X		X
Diary Completion		X	
Adverse Event Assessment		X	X
Concomitant Medications Assessment	X	X	X
Telephone Contact		X[3]	X
Source Document and eCRF Completion	X		X

[1] The End of Study Visit should occur within 7 days after the subject treats up to his/her third headache or within 7 days after the completion of the 84-day treatment period, whichever occurs first.

[2] Subjects will return to the clinic at 4 and 8 weeks after the Screening Visit as necessary for a replacement dispenser.

[3] Subjects will be contacted by telephone within 3 days of treating their 1st attack to answer any questions, assess if there are any problems with compliance or any concerning AEs.

9.0 ASSESSMENT OF SAFETY

9.1 General Guidelines

All AEs (NSAEs and SAEs), regardless of causality or severity, will be recorded in the subject's AE eCRF document according to Section 8.1.11. Appropriate medical intervention should be provided if required.

9.2 Definitions

The following definitions, developed in accordance with the International Committee on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, and 21 CFR Parts 312.32 and 812.3 will be used for the purpose of identifying AEs in this clinical study.

9.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject, or clinical investigation subject, administered a pharmaceutical product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or increase in severity or frequency of a pre-existing abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

9.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is reasonable possibility that the drug caused the adverse event. Suspected adverse reactions will consist of the adverse events that are evaluated by the investigator as possibly related or probably related to the study drug and/or study device.

9.2.3 Serious Adverse Event

A serious adverse event (SAE) is any adverse experience occurring after randomization at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital anomaly/birth defect (in an offspring)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.3.1 Hospitalizations as Serious Adverse Events

All AEs requiring hospitalization or prolongation of hospitalization should be reported as SAEs.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, or elective hospitalizations.

9.2.4 Unanticipated Adverse Device Effect

A serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.3 Reporting of Safety Information

9.3.1 Adverse Event Reporting

All AEs, regardless of causality, severity, whether expected or not, must be entered on the AE CRF. Disease-related signs and symptoms that are present at baseline should not be reported as AEs unless they worsen in severity or frequency. Information collected concerning AEs will include the following:

- Name of the event

- Start date

- Stop date or if the event is continuing

- Intensity

- Mild (does not interfere with subject's usual function)
- Moderate (interferes to some extent with the subject's usual function)
- Severe (interferes significantly with subject's usual function)

- Relationship to investigational product (drug, device or both)
- Seriousness of event
- Outcome
- Action taken

Non-serious adverse events will be collected beginning after the first dose of study medication through the End of Study Visit and will include any change from the subject's condition at Screening. All NSAE that are deemed related to study drug and/or study device will be followed until resolution or stabilization of the event. SAEs will be collected following enrollment and will include any change from the subject's baseline condition at Screening. SAE collection will conclude at End of Study or until resolution of the SAE if it extends beyond the End of Study Visit.

9.3.2 Serious Adverse Event Reporting

All SAEs must be reported to Capnia within 24 hours of first knowledge of the event. All SAEs that occur from the time the subject is enrolled through the End of Study Visit are reportable within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of first knowledge of the event, the site must contact Capnia by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Initial reporting should not be delayed in order to obtain resolution or follow-up information.
- The site will fax an SAE report, or similar form, that includes the following information, as available:
  - Subject ID
  - Basic demographic information (age, gender, weight)

- Relationship to investigational product (drug, device or both)
- The outcomes attributed to the event (death, life-threatening, hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)
- The onset date and severity of the event
- A brief description of the event including frequency and severity of symptoms leading to diagnosis
- A list of relevant test results and lab data
- Any other relevant history
- Date of investigational product administration
- Whether the investigational product was discontinued prematurely
- Investigator's assessment of causality

The completed SAE report should be faxed as soon as possible (within 24 hours) to:

CAPNIA, Inc.
Attn: Anish Bhatnagar, MD
1235 Radio Road, Suite 110
Redwood City, CA 94065 USA
(+1) 650-213-8444 ext. 19 Telephone
(+1) 650-619-3449 Mobile
(+1) 866-286-1332 Fax

Dr. Bhatnagar or another representative of Capnia may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE eCRF. The same nomenclature should be used on both the SAE report and the AE CRF.

The Investigator is responsible for the complete and timely reporting of all SAEs to Capnia, following up on resolution of the SAE, and expeditiously and simultaneously notifying the responsible IRB of the occurrence and details of the event according to institutional standard procedures. In the event there is a question as to whether the experience is serious, the event should be reported.

9.4 Adverse Event Follow-up

All AEs that are deemed by the Investigator to be related to study drug and/or study device will be followed until resolution or stabilization of the event.

10.0 STATISTICAL METHODS AND ANALYSIS

10.1 General Considerations

Tests will be conducted with a two-sided alpha = 0.05. Descriptive statistics and 95% confidence intervals will be presented with all analyses.

One interim analyses will be performed after 12 subjects have completed the study. All efficacy and safety analyses will be performed at the conclusion of the study.

10.2 Handling of Dropouts or Missing Data

Efficacy analyses (primary and key secondary endpoints) may be performed using the last value carried forward (LVCF) method.

LVCF will be used only for pain scores up to the specified time point that occurred after the first headache treated with the study drug. All other analysis will be performed on observed values. The following rules will be applied for LVCF method for pain scores:

- If there is only baseline headache pain score available prior to rescue or prior to missing headache pain score, the baseline value will be carried forward as the LVCF.

10.3 Endpoints

10.3.1 Primary Efficacy Endpoint

Greatest change from pre-treatment headache pain intensity to post treatment at any time point within 30 minutes of Nasal CO_2 administration.

10.3.2 Method and Timing of Assessing Efficacy

Since this is an open-label, pilot study, all efficacy analyses will be performed after 12 subjects have treated at least 1 cluster attack.

10.3.3 Secondary Efficacy Endpoints

The key secondary endpoints are:

- Percentage of subjects experiencing headache pain freedom at 5-60 minutes within the treated attack
- Percentage of subjects with headache relief at 5-60 minutes within the treated attack
- Rescue medication usage
- Subject satisfaction
- Cluster recurrence

This analysis will be assessed for the first headache treated with the investigational product.

10.3.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be assessed for the first headache and for all headaches.

Exploratory efficacy endpoints include:

- Number of doses per attack
- Consistency of response with repeated treated attacks

All primary, secondary, and exploratory efficacy endpoints will be analyzed for the all headaches analyses as well.

The endpoint for extent of exposure will be the number of doses per subject per headache.

10.3.5 Safety Endpoint

The safety endpoints are adverse events and concomitant medications. Additional safety assessments will include changes from baseline in nasal mucosa.

10.4 Analysis Sets

10.4.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population will consist of all subjects enrolled in the study. The ITT population will primarily be used to describe subject disposition and baseline characteristics.

10.4.2 Modified Intent-to-Treat (mITT) Population

The modified intent to treat (mITT) population will consist of all ITT subjects who treated a headache, received at least one dose of the study drug, and had at least one post treatment efficacy evaluation. The mITT population will be used to conduct all efficacy analyses.

10.4.3 Per Protocol (PP) Population

The per protocol (PP) population is defined as all mITT subjects who had no major protocol violations. Subjects will be analyzed based on the treatment that they actually received. The PP population will be used to analyze the primary and key secondary efficacy endpoints.

10.4.4 Safety Analysis Set

The safety analysis set will consist of all subjects enrolled in the study who receive at least one administration of investigational product. The safety population will be used for all safety analyses.

10.5 Primary Efficacy Analysis

This analysis will be performed using the mITT population. This analysis will be assessed for the first headache treated with the investigational product and all headaches treated as well.

10.6 Secondary Efficacy Analyses

No adjustments will be made for multiplicity in the analyses of the secondary efficacy endpoints.

This analysis will be performed using the mITT population. This analysis will be assessed for the first headache treated with the investigational product and all headaches treated as well.

10.7 Exploratory Efficacy Analyses

No adjustments will be made for multiplicity in the analyses of the exploratory efficacy endpoints.

This analysis will be performed using the mITT population. This analysis will be assessed for the first headache treated with the investigational product and all headaches treated as well.

The extent of exposure will be compared between the two treatment groups descriptively for the first headache as well as the all headaches analysis.

10.8 Safety Analysis

All safety analyses will be performed on all enrolled subjects.

10.8.1 Adverse Events

Adverse events (AEs) will be monitored throughout the study. All reported AEs will be documented on the appropriate eCRF. All similar AEs will be combined into one category and the frequency of all AEs occurring above 5% will be reported.

10.8.2 Vital Signs

Vital signs will be summarized using descriptive statistics.

10.8.3 Concomitant Medications

Concomitant medications, as well as rescue medications, will be summarized using descriptive statistics.

10.8.4 Other Observations Related to Safety

Physical, neurological, and nasal examination results, as well as other observations related to safety will be summarized in data listings.

10.9 Termination Criteria

Based on studies conducted with nasal CO_2 to date, it is not expected that serious safety issues will arise that would require the sponsor to discontinue parts or all of the study. If such issues do arise, the sponsor will, in consultation with Capnia, appropriate regulatory authority, and IRB take the steps necessary to discontinue the study.

There will be an ongoing analysis of the data, and as such there is the possibility of terminating the study early due to efficacy or lack of efficacy.

10.10 Accountability Procedure

For primary efficacy analyses, no adjustment for missing values will be made. Exploratory analyses may be performed using the last value carried forward (LVCF) method.

10.11 Deviation Reporting

Any significant deviations to the statistical analysis plan (Sections 10.1 through 10.11) will be addressed in the final report for this study.

11.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

During the trial, Clinvest will conduct remote monitoring and safety oversight periodically. The clinical monitors may review eCRFs, at intervals throughout the study to verify appropriate inclusion of subjects, adherence to the protocol, and completeness, correctness, and accuracy of eCRF entries. Any source upload should be reviewed for privacy elements and removed. Source uploads should only include the subject enrollment number as identifying information.

The Investigator and Institution will permit authorized representatives of Capnia, its designees, the national health authorities, local authorities, and IRB direct access to source data/documents to conduct study-related monitoring, audits, IRB review, and regulatory inspections.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

It is Clinvest's responsibility for implementing and maintaining quality control and assurance with written SOPs to ensure the trial is conducted in compliance with GCP standards and all applicable federal, state, and local laws, rules, and regulations. Appropriate tools will be implemented by the site to facilitate quality management of the subject and continuity through the trial.

Quality control should be applied by all parties and to each stage of subject management, investigational product management and data handling to ensure all data are reliable and have been processed correctly. All clinical data are to be generated and processed by personnel with relevant clinical and GCP knowledge. Subject generated data should be preceded with appropriate subject training and technical support for questions that arise during the trial.

Agreements, made by Clinvest, the investigator, and Capnia, Inc. and/or with any other parties involved with clinical trial should be in writing in a separate agreement.

Capnia, Inc. has provided Clinvest a Letter of Authorization so that Clinvest may cross-reference, Capnia INDs #74,680 and 126,801. As the investigator-sponsor of this study, the ultimate responsibility for the quality and integrity of the trial data also resides with Clinvest. The investigator agrees to be responsible for the integrity of all study conduct at their site.

The study will be registered on ClinicalTrials.gov by Clinvest.

13.0 ETHICAL CONSIDERATIONS

This study will be conducted according to the applicable regulations and international standards of GCP.

All subjects for this study will be provided an informed consent form describing this study and providing sufficient information for subjects to make an informed decision about their

participation in this study. This consent form will be submitted with the protocol for review and approval by the appropriate IRB. The formal consent of a subject, using the IRB-approved informed consent form, will be obtained before that subject undergoes any study-specific procedure. This informed consent form must be signed by the subject or legally acceptable surrogate, and the Investigator-designated research professional obtaining the informed consent.

14.0 DATA HANDLING AND RECORD KEEPING

Data for this trial will be primarily collected in a web-based electronic data capture (EDC) REDCap platform. The EDC access will be supplied by Clinvest with relevant training support to sites. The site will be responsible for training study subjects in the EDC system. All data specified should be captured by the site personnel or subjects in the EDC system. All eCRFs are to be completely filled out by personnel administering the study procedures at the time of the visit. The eCRF will be considered the source document for all data collected other than laboratory and procedure findings, which will be uploaded into the eCRF as source. All data must be reviewed and signed by the investigator or sub-investigator at the conclusion of the study for each subject. The eCRFs should not be made available in any form to third parties, without written permission from the sponsor.

It is the investigator's responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF and confirmation the data is accurate, authentic, attributable, complete, and consistent. The investigator or sub-investigator must sign the eCRFs within the EDC system to attest the information contained with the eCRF is true and causality of any safety information has been assessed.

Study documentation includes all workbooks, worksheets, forms, lab reports, logs, signature pages, appointment schedules, investigator correspondence, electronic data (i.e. data stored on cds, flash drives, etc.), and regulatory documents. The original recording of an observation should be retained as the source document.

1. Investigator will maintain essential documents for the conduct of a clinical study and any other documentation as specified by applicable regulatory requirements.

2. Investigator will maintain a binder containing written informed consent records.

3. Conduct of study visits will be maintained on appropriate Source Documentation/Case Report Forms. Subject anonymity will be maintained on these forms by identification codes (i.e., subject initials and number). The Investigator's electronic signature will verify that all data entries in the CRF's are complete and accurate.

4. Investigator will maintain a Subject Identification Log. Information such as full name of subject, address, contact information, and additional subject identifiers will be recorded. This log will be kept confidential and not copied.

5. Investigator will maintain a Subject Screening/Enrollment Record. This record will record chronologically subjects who were seen for Screening/Enrollment, additional visits conducted to replace Nasal CO_2 dispensers, and completion/discontinuation information.

6. Clinvest will maintain an Investigational Product Assignment Log. This log will record chronologically study medication received from Capnia, Inc. as well as medication returned or destroyed at the completion of the study.

Government agency regulation and directives require all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator for at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The investigator will maintain all study documentation on file in a secure and safe location. Clinvest will notify the investigator in writing when retention is no longer necessary. No study records will be destroyed without prior agreement between Capnia, Inc. and Clinvest.

15.0 REFERENCE LIST

1. Vause C, Bowen E, Spierings E, Durham P. Effect of carbon dioxide on calcitonin gene-related peptide secretion from trigeminal neurons. *Headache.* Nov-Dec 2007;47(10):1385-1397.
2. Bennett MH, French C, Schnabel A, Wasiak J, Kranke P. Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. *The Cochrane Database of Systematic Reviews.* 2008(3):CD005219.
3. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia.* Jul 2013;33(9):629-808.
4. Friedman BW, Grosberg BM. Diagnosis and management of the primary headache disorders in the emergency department setting. *Emergency Medicine Clinics of North America.* Feb 2009;27(1):71-87, viii.
5. Pringsheim T. Cluster headache: evidence for a disorder of circadian rhythm and hypothalamic function. *Can J Neurol Sci.* Feb 2002;29(1):33-40.
6. Lainez MJ, Puche M, Garcia A, Gascon F. Sphenopalatine ganglion stimulation for the treatment of cluster headache. *Therapeutic Advances in Neurological Disorders.* May 2014;7(3):162-168.
7. D'Amico D, Rigamonti A, Solari A, et al. Health-related quality of life in patients with cluster headache during active periods. *Cephalalgia.* Dec 2002;22(10):818-821.
8. Tzabazis AZ, Niv SH, Manering NA et al. Trigeminal antihyperalgesic effect of intranasal carbon dioxide. *Life Sci* 2010;87:36-41.
9. Casale TB, Romero FA, Spierings EL. Intranasal noninhaled carbon dioxide for the symptomatic treatment of seasonal allergic rhinitis. *The Journal of Allergy and Clinical Immunology.* Jan 2008;121(1):105-109.
10. Casale T, Onder R, Berkowitz R, Yen K, Bhatnagar A, Korenblat P. Nasal non-inhaled carbon dioxide for as-needed treatment of rhinitis symptoms [abstract]Casale T, Onder R, Berkowitz R, Yen K, Bhatnagar A, Korenblat P. *Allergy* 2010;65:35