BOTULINUM TOXIN DOSAGE REGIMEN FOR CHRONIC MIGRAINE PROPHYLAXIS

Cross Reference to Related Applications

[1] This application claims the benefit of U.S. Provisional Application Ser. No.'s 61/319,230, filed March 30, 2010, and 61/320,667, filed April 2, 2010, all incorporated entirely by reference.

Field

[2] Embodiments of the present invention relate to the treatment of various disorders, specifically to injection administration protocols utilizing botulinum neurotoxin.

Background

[3] It is known that botulinum toxins can be utilized to treat a variety of disorders. Examples include U.S. Patent 5,714,468 (migraine) issued February 3, 1998; Published U.S. Patent Application No. 2005019132 (headache), serial number 11/039,506, filed January 18, 2005; Published U.S. Patent Application No. 20050191320 (medication overuse headache), serial number 10/789,180, filed February 26, 2004; and U.S. Patent 7,811,587 (neuropsychiatric disorders), issued October 12, 2010; all incorporated entirely by reference.

[4] An example of a disorder treatable with botulinum toxins is chronic migraine (CM), a disabling headache disorder, affecting 1.3% to 2.4% of the general population and considered the most common type of primary chronic daily headache in the United States. CM is linked with suffering, disability, and medication overuse, and only one third of CM patients use headache prophylactic medication. Few headache preventive treatments have been investigated for patients with CM. Thus there remains a need for optimized and targeted methodologies to treat this malady in particular, specific and useful injection and dosage paradigms for utilizing botulinum toxins to treating CM.

[5] Another condition amenable to treatment with botulinum toxin is Medication Overuse Headache Disorder (MOU). It has been described as a self-sustaining, rhythmic, headache medication cycle characterized by daily or near daily headache with irresistible and predictable use of immediate relief medications. Evidence supporting the existence of MOH is widely published in the medical literature.

Summary

[6] In one embodiment, the present invention teaches a method for prophylactically treating a headache in a patient suffering from chronic migraine headaches, the method essentially consisting of local administration of a botulinum neurotoxin to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of the patient that suffers from the migraine headache, where the botulinum neurotoxin is administered, to the frontalis at about twenty units divided among four sites of injection, to the corrugator at about ten units divided among two sites of injection; to the procerus at about five units to one site of injection; to the occipitalis at about thirty units divided among six sites of injection to about forty units divided among eight sites of injection; to the temporalis at about forty units divided among eight sites of injection up to fifty units divided among ten sites of injection; to the trapezius at about thirty units divided among six sites of injection up to about fifty units divided among ten sites of injection and to the cervical paraspinal muscles at about twenty units divided among four sites of injection, and where the botulinum neurotoxin is injected at 31 to 39 injection sites.

Brief Description of the Figures

[7] The following drawings are presented to illustrate aspects and features of embodiments of the present invention.

[8] Figure 1 is a graph showing the results (mean change in the number of headaches per thirty day period) of a clinical study carried out for use of BOTOX® to *inter alia* treat migraine headache, showing that the patients had fewer headaches after administration of BOTOX®. In the data shown in the Figures, the patients had been administered BOTOX® at days 0, 90 and 180.

[9] Figure 2 is a graph showing the results (mean change in the number of days patients were concurrently taking acute headache pain alleviation medication per thirty day period) of a clinical study using BOTOX® to *inter alia* treat migraine headache, showing that the patients had fewer days when they were taking acute headache pain alleviation medication after administration of BOTOX®.

[10] Figure 3 is a graph showing a comparison of the percent of patients (some who had been administered BOTOX® and some who had been administered a placebo) who were over a

thirty day period using narcotics medication to control acute headache pain. Figure 3 shows a decrease in narcotic use in the BOTOX®-treated patients.

[11] Figure 4 is a graph showing a decrease in the percentage of patients who had acute headache medication overuse in a thirty day period after administration of BOTOX®.

[12] Figure 5 is a graph showing a decrease in the percentage of patients who had demonstrated overuse of triptans in a thirty day period after administration of BOTOX®.

[13] Figure 6 comprises two graphs showing the mean change in the number of headaches experienced by patients over a thirty day period after administration of BOTOX®, where the patients either did not have MOU ("without MOU"; left side graph) or the patients did have an MOU disorder (right side graph). "≥15 days and ≥2days/week" are criteria used to determine that a patient had an MOU disorder. MOU and MOD are synonymous terms. By definition, a patient has an MOU disorder if he or she takes an acute medication 15 or more days per month and at least twice a week in the week that they are experiencing the acute pain.

[14] Figure 7 comprises two graphs which show the mean change from baseline in the frequency of headaches per 30-day period in patients using (graph A) and not using (graph B) prophylactic headache medications at baseline, for a pooled population of patients. The Y-axis represents the mean change in the number of headaches per thirty day period. "n" indicates the number of patients in the sample of patients evaluated.

[15] Figure 8 comprises two graphs which show the mean change in the number of headaches experienced by patients over a thirty day period after administration of BOTOX®, where the patients either were not concurrently using another headache prophylaxis treatment (left side graph) or the patients were not concurrently using another headache prophylaxis treatment and did have an MOU disorder (right side graph).

[16] Figure 9 comprises two graphs showing the mean change in the number of headaches experienced by patients over a thirty day period after administration of BOTOX®, where the patients either were not concurrently using another headache prophylaxis treatment and did not have an MOU disorder (left side graph) or the patients were not concurrently using another headache prophylaxis treatment and did have an MOU disorder (right side graph).

[17] Figure 10 is a bar chart showing the percentage of patients over a thirty day period after administration of BOTOX® who were also using an opioid acute headache medication.

[18] Figure 11 comprises two graphs which show the mean change in the number of headaches experienced by patients over a thirty day period after administration of BOTOX®, where the patients either were triptan medication overuse patients (left side graph) or not triptan medication overuse patients (right side graph).

[19] Figure 12 comprises two graphs which shows the mean change from baseline (after administration of BOTOX®) in number of days with acute headache (analgesic) medication use by the patients, where the patients were either triptan medication overuse patients (left side graph) or not triptan medication overuse patients (right side graph).

[20] Figure 13 comprises on the left side, a left side diagrammatic view of human muscle anatomy from the shoulders up, and on the right side a diagrammatic view of the back.

[21] Figure 14 comprises two graphs which show the mean change from baseline in the frequency of headaches per 30-day period for placebo non-responders (A) and responders (B).

[22] Figure 15 shows the mean change from baseline in the frequency of headaches per 30-day period, for a pooled population of patients.

[23] Figure 16 comprises two graphs which show mean change from baseline in the number of days of use of acute analgesic headache medications per 30-day period for patients using (graph A) and not using (graph B) prophylactic headache medications at baseline, for a pooled population of patients.

[24] Figure 17 depicts an example of fixed locations to which doses of botulinum toxin are administered to a patient (here in supine and sitting positions) in accordance with one embodiment of an injection paradigm.

Description

[25] In certain embodiments, the dose of a botulinum toxin used according to embodiments of the present invention is less than the amount of botulinum toxin that would be used to paralyze a muscle, because an intent of a method according to embodiments of the present invention is not to paralyze a muscle but to reduce a pain sensory output from sensory neurons located in or on a muscle, or in or under the skin.

[26] The following definitions apply herein:

[27] "About" means approximately or nearly and in the context of a numerical value or range set forth herein means ±10% of the numerical value or range recited or claimed.

[28] "Alleviating" means a reduction in the occurrence of a pain, of a headache or of a symptom of a headache. Thus, alleviating includes some reduction, significant reduction, near total reduction, and total reduction. An alleviating effect may not appear clinically for between 1 to 7 days after administration of a Clostridial toxin to a patient or sometime thereafter.

[29] "Botulinum toxin" means a botulinum neurotoxin as either pure toxin or complex, native, recombinant, or modified, and includes botulinum toxin type A, type B, type C_1, type D, type E, type F, and type G. As used herein, this term excludes non-neurotoxins, such as the cytotoxic botulinum toxins C_2 and C_3.

[30] "Local administration" means administration of a pharmaceutical agent to or to the vicinity of a muscle or a subdermal location in a patient by a non-systemic route. Thus, local administration excludes systemic routes of administration, such as intravenous or oral administration.

[31] "Peripheral administration" means administration to a location away from a symptomatic location, as opposed to a local administration.

[32] "MOU" means medication overuse headache or medication overuse headache disorder.

[33] "Treating" or "treatment" means to alleviate (or to eliminate) at least one symptom (such as, for example, headache pain), either temporarily or permanently. This can include prophylactic applications to prevent at least one symptom of headache.

[34] Disclosed herein are embodiments of an administration paradigm for botulinum neurotoxins. In some embodiments, the method can include specific injection locations and dosage amounts of botulinum toxin to treat various disorders, including, for example, CM, MOU, ND's, and the like. In certain embodiments of the invention, the disorder can be treated by intramuscular administration of the toxin in specific amounts or ranges of amounts to specific sites within the upper torso of the patient. In certain embodiments, such sites can include, for example, the head, the neck, one or both shoulders, in both the anterior or posterior positions. The botulinum toxin can be a botulinum toxin type A, type B, type C_1, type

D, type E, type F, or type G, or any combination thereof. The botulinum neurotoxin can be a recombinantly made botulinum neurotoxins, such as botulinum toxins produced by *E. coli*.

[35] In addition, the botulinum neurotoxin can be a modified neurotoxin, that is a botulinum neurotoxin which has at least one of its amino acids deleted, modified or replaced, as compared to a native toxin, or the modified botulinum neurotoxin can be a recombinant produced botulinum neurotoxin or a derivative or fragment thereof. In certain embodiments, the modified toxin has an altered cell targeting capability for a neuronal or non-neuronal cell of interest. This altered capability is achieved by replacing the naturally-occurring targeting domain of a botulinum toxin with a targeting domain showing a selective binding activity for a non- botulinum toxin receptor present in a non- botulinum toxin target cell. Such modifications to a targeting domain result in a modified toxin that is able to selectively bind to a non-botulinum toxin receptor (target receptor) present on a non-botulinum toxin target cell (re-targeted). A modified botulinum toxin with a targeting activity for a non-botulinum toxin target cell can bind to a receptor present on the non-botulinum toxin target cell, translocate into the cytoplasm, and exert its proteolytic effect on the SNARE complex of the target cell. In essence, a botulinum toxin light chain comprising an enzymatic domain is intracellularly delivered to any desired cell by selecting the appropriate targeting domain.

[36] Botulinum toxins for use according to the present invention can be stored in lyophilized, vacuum dried form in containers under vacuum pressure or as stable liquids. Prior to lyophilization the botulinum toxin can be combined with pharmaceutically acceptable excipients, stabilizers and/or carriers, such as, for example, albumin, or the like. In embodiments containing albumin, the albumin can be, for example, human serum albumin, or the like. The lyophilized material can be reconstituted with a suitable liquid such as, for example, saline, water, or the like to create a solution or composition containing the botulinum toxin to be administered to the patient.

[37] The amount of the botulinum toxin administered according to a method within the scope of embodiments of the invention can vary according to the particular characteristics of the pain being treated, including its severity and other various patient variables including size, weight, age, and responsiveness to therapy. To guide the practitioner, typically, no less than about 1 unit and no more than about 25 units of a botulinum toxin type A (such as BOTOX®) is administered per injection site per patient treatment session. For a botulinum toxin type A

such as DYSPORT®, no less than about 2 units and no more than about 125 units of the botulinum toxin type A are administered per injection site, per patient treatment session. For a botulinum toxin type B such as MYOBLOC®, no less than about 40 units and no more than about 1500 units of the botulinum toxin type B are administered per injection site, per patient treatment session.

[38] Preferably, for BOTOX® no less than about 2 units and no more about 20 units of a botulinum toxin type A are administered per injection site per patient treatment session; for DYSPORT® no less than about 4 units and no more than about 100 units are administered per injection site per patient treatment session;, and; for MYOBLOC®, no less than about 80 units and no more than about 1000 units are administered per injection site, per patient treatment session.

[39] More preferably, for BOTOX® no less than about 5 units and no more about 15 units of a botulinum toxin type A; for DYSPORT® no less than about 20 units and no more than about 75 units, and; for MYOBLOC®, no less than about 200 units and no more than about 750 units are, respectively, administered per injection site, per patient treatment session.

[40] Generally, the total amount of BOTOX® , DYSPORT® or MYOBLOC®, suitable for administration to a patient according to the methods of the invention disclosed herein should not exceed about 300 units, about 1,500 units or about 15,000 units respectively, per treatment session.

[41] The treatment effects of the botulinum toxin can persist for between about 1 month and 5 years.

[42] Embodiments of the invention provide a targeted, fixed injection paradigm directed to a specific set of muscles with a specific minimum number and volume of injections, and further provides for the additional/optional administration of additional botulinum toxin to specific site of selected muscles. In one embodiment, the fixed dosage (that is, a minimum dosage amount in accordance with the fixed amounts and locations specified in a package insert or prescribing information) of botulinum toxin is administered to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of a patient, and further a variable amount of additional botulinum toxin can be added to four or less of the seven head/neck areas such that the total amount of botulinum toxin administered does not exceed a

maximum total dosage as indicated in the package insert or prescribing information accompanying a botulinum toxin-containing medicament. The botulinum toxin can be selected from the group consisting of botulinum toxin types A, B, C, D, E, F and G. Botulinum toxin type A is a preferred botulinum toxin. The botulinum toxin can be administered in an amount of between about 1 unit and about 3,000 units, or between about 2 units and about 2000 units, or between about 5 units and about 1000 units, or between about 10 units and about 500 units, or between about 15 units and about 250 units, or between about 20 units and about 150 units, or between 25 units and about 100 units, or between about 30 units and about 75 units, or between about 35 units and about 50 units, or the like, and the alleviation of the symptoms can persist for between about 1 month and about 5 years.

[43] In one embodiment, a method is disclosed that utilizes a dose and injection paradigm of 155 units of BOTOX® (typically provided as 100 Units of *Clostridium botulinum* type A neurotoxin complex, with 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride in a sterile, vacuum-dried state for reconstitution), administered as 31 fixed-site, fixed-dose (5 units per) injections, and an optional 40 units in up to 8 additional injection sites using a follow-the-pain regimen per treatment cycle (for up to 39 injection sites and up to 195 units total). The total dose is divided across 7 head/neck muscles and is repeated every 12 weeks.

[44] In an embodiment, a method for treating a migraine such as, for example, CM, can encompass administration of a botulinum toxin to 31 fixed injection sites across seven head/neck muscles. Optionally, up to 8 additional injection sites into three specific muscles, where these three muscles are subset of the above seven head/neck muscles, are administered utilizing a follow-the pain regimen to provide flexibility in the dose/muscle for the three muscles, to address individual patient needs. In particular embodiments, a minimum of 155 units of a botulinum toxin type A up to about 195 units of a botulinum toxin type A, are administered in accordance with a particular injection paradigm herein disclosed.

[45] In a specific embodiment, a method for treating CM comprises the step of local administration of a botulinum neurotoxin to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of the CM patient such that the botulinum neurotoxin is administered to the frontalis at about twenty units divided among four sites of injection, to the corrugator at about ten units divided among two sites of injection, to the procerus at about five units to one site of injection, to the occipitalis at about thirty units

divided among six sites of injection to about forty units divided among eight sites of injection; to the temporalis at about forty units divided among eight sites of injection up to fifty units divided among ten sites of injection, to the trapezius at about thirty units divided among six sites of injection up to about fifty units divided among ten sites of injection and to the cervical paraspinal muscles at about twenty units divided among four sites of injection, such that the total amount of botulinum neurotoxin administered is from about 155 units to about 195 units injected at from 31 to 39 injection sites, respectively.

[46] In one aspect, embodiments of the present invention are based on the discovery that a botulinum toxin can be used to treat a patient with MOU to reduce both (a) the number of headaches experienced by the patient (see Figure 1) and (b) the daily use of acute headache pain medication by the patient (Figure 2). In particular we have found (*see* Figure 3) that a botulinum toxin can be used to reduce use by patients of narcotic pain medication.

[47] Additionally, we found that patients who were overusing pain alleviation medication experienced a significant reduction in their use of such medications after treatment with a botulinum toxin (*see* Figure 4). We also found that there was a significant reduction in the intake of triptan medications in triptan medication overuse patients (*see* Figure 5).

[48] Embodiments of the invention can also be used as part of a detoxification protocol whereby a patient who is being weaned off acute pain medications is facilitated in this goal by concurrent administration of a botulinum toxin. Additional embodiments of the invention can be used to treat other chronic pain conditions, including, for example, back pain, neuropathic pain, allodynia, fibromyalgia, and the like.

[49] In an embodiment, a method for treating an MOU patient can encompass administration of a botulinum toxin to 31 fixed injection sites across seven head/neck muscles. Optionally, up to 8 additional injection sites into three specific muscles, where these three muscles are subset of the above seven head/neck muscles, are administered utilizing a follow-the pain regimen to provide flexibility in the dose/muscle for the three muscles, to address individual patient needs. In particular embodiments, a minimum of 155 units of a botulinum toxin type A up to about 195 units of a botulinum toxin type A, are administered in accordance with a particular injection paradigm herein disclosed.

[50] In a specific embodiment, a method for treating MOU comprises the step of local administration of a botulinum neurotoxin to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of the MOU patient such that the botulinum neurotoxin is administered to the frontalis at about twenty units divided among four sites of injection, to the corrugator at about ten units divided among two sites of injection, to the procerus at about five units to one site of injection, to the occipitalis at about thirty units divided among six sites of injection to about forty units divided among eight sites of injection; to the temporalis at about forty units divided among eight sites of injection up to fifty units divided among ten sites of injection, to the trapezius at about thirty units divided among six sites of injection up to about fifty units divided among ten sites of injection and to the cervical paraspinal muscles at about twenty units divided among four sites of injection, such that the total amount of botulinum neurotoxin administered is from about 155 units to about 195 units injected at from 31 to 39 injection sites, respectively.

[51] In an embodiment, a method for treating depression can encompass administration of a botulinum toxin to 31 fixed injection sites across seven head/neck muscles. Optionally, up to 8 additional injection sites into three specific muscles, where these three muscles are subset of the above seven head/neck muscles, are administered utilizing a follow-the pain regimen to provide flexibility in the dose/muscle for the three muscles, to address individual patient needs. In particular embodiments, a minimum of 155 units of a botulinum toxin type A up to about 195 units of a botulinum toxin type A, are administered in accordance with a particular injection paradigm herein disclosed.

[52] In a specific embodiment, a method for treating ND's such as, for example, depression, in a patient in need thereof comprises the step of local administration of a botulinum neurotoxin to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of the patient such that the botulinum neurotoxin is administered to the frontalis at about twenty units divided among four sites of injection, to the corrugator at about ten units divided among two sites of injection, to the procerus at about five units to one site of injection, to the occipitalis at about thirty units divided among six sites of injection to about forty units divided among eight sites of injection; to the temporalis at about forty units divided among eight sites of injection up to fifty units divided among ten sites of injection, to the trapezius at about thirty units divided among six sites of injection up to about fifty units divided

among ten sites of injection and to the cervical paraspinal muscles at about twenty units divided among four sites of injection, such that the total amount of botulinum neurotoxin administered is from about 155 units to about 195 units injected at from 31 to 39 injection sites, respectively.

[53] Significantly, a method within the scope of the present invention can provide improved patient function. "Improved patient function" can be defined as an improvement measured by factors such as a reduced pain, reduced time spent in bed, increased ambulation, healthier attitude, more varied lifestyle and/or healing permitted by normal muscle tone. Improved patient function is may be measured with an improved quality of life (QOL) or Health-Related Quality of Life (HRQL). QOL can be assessed, for example, using the SF-12 or SF-36 health survey scoring procedures, or the Migraine Specific Quality of Life Questionnarie (MSQ). SF-36 assesses a patient's physical and mental health in the eight domains of physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality and general health perceptions. Scores obtained can be compared to published values available for various general and patient populations. The Migraine-Specific Quality of Life Questionnaire Version 2.1 is one of the most frequently utilized disease-specific tools assessing the impact of migraine on HRQL. The MSQ measures the impact of migraine on the patient's HRQL over the past 4 weeks across three dimensions: Role Function-Restrictive (RR), Role Function-Preventive (RP), and Emotional Function (EF). The MSQ was developed from an expert-based item review of the migraine literature and validated in a clinical sample of 458 new and stable EM patients. In the validation study the MSQ revealed high internal consistency (Cronbach's α=.79 to.85), a moderate to strong convergent validity, as well as an adequate discriminant validity. Martin and Colleagues 21 performed a multi-center study that further supported the evidence of a high internal consistency (Cronbach's α =.86 to .96), strong reliability and good validity of the 14-item MSQ among 267 participants.

[54] The following non-limiting examples provide those of ordinary skill in the art with specific preferred methods to treat chronic migraine within the scope of the present disclosure, and it is not intended to limit the scope of the invention. In the following examples various modes of non-systemic administration of a Clostridial neurotoxin can be carried out. For

example, by intramuscular injection, subcutaneous injection or by implantation of a controlled release implant.

EXAMPLES

[55] The following non-limiting examples provide those of ordinary skill in the art with specific preferred methods to treat conditions within the scope of embodiments of the present invention and are not intended to limit the scope of the invention.

[56] Example 1 - Botulinum Toxin Type A Therapy for Headache Pain Associated with Chronic Migraine

[57] In similarly designed, multicenter, randomized, placebo-controlled, phase 3 trials, 1384 adults with CM were randomized to onabotulinumtoxinA (botulinum toxin type A) (n=688) or placebo (n=696). Both studies consisted of a 28-day baseline screening period (hereafter referred to as baseline), a 24-week, double-blind (DB) phase (2 injection cycles), and a 32-week, open-label (OL) phase (3 treatment cycles). Study visits occurred every 4 weeks and patients used a daily telephone diary to record their headache symptoms and acute pain medications. Participants were men or women aged 18 to 65 years with a history of migraine meeting the diagnostic criteria listed in ICHD-II (2004) Section 1, Migraine, with the exception of "complicated migraine," and with headache occurring ≥15 days/month with at least 50% of the headache days being migraine or probable migraine days.

[58] Botulinum toxin type A blocks the release of neurotransmitters associated with pain genesis. As confirmed by preclinical and clinical trials, the presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, inhibiting central sensitization. The fixed-site approach herein disclosed targets distribution of botulinum toxin type A to muscles and skin in the innervation distribution of V1 and C2 nerves.

[59] Based on analyses of the safety, tolerability, and efficacy of the dosing paradigms explored in previous studies, the instant injection paradigm was developed. In this example, the particular botulinum neurotoxin utilized is onabotulinumtoxinA (BOTOX® Allergan Inc. Irvine CA). Injection targets included the following muscles:

[60] Frontalis, Corrugator, and Procerus: In the previous trials, patients most often reported the frontal/glabellar region as the origin and end of their headache; these and other trials showed that all 3 muscles needed injections for maximum efficacy.

[61] Temporalis: In previous trials, the temporalis region was the second most frequent location cited as the start and end of head pain. In accordance with one aspect of the instant disclosure, a minimum dose of 20 units per side and up to an additional 10 units (follow-the-pain strategy) total (administered to 1 or both sides in 5 unit increments) is administered to this muscle.

[62] Cervical Paraspinal Muscles: In previous trials, patients indicated that their headache pain frequently started and/or stopped in the back of the head (in the occipitalis and/or the neck). To maintain efficacy and improve overall tolerability (lower incidence of neck pain, neck rigidity, and neck muscle weakness), in one aspect the instant injection paradigm includes the recommendations of: (a) giving injections to the upper neck (cervical paraspinal muscles) at the base of the skull; (b) do not utilize a follow-the-pain injection regimen in the neck area; (c) keep injections superficial and (d) reduce the total dose injected to the neck region to a fixed-site, fixed-dose of 20 units total for this muscle group (10 units to each side of the head). Accordingly, it was shown that this dose adjustment was successful and safe, as only 1 patient here needed to use a soft collar compared to 10 in previous studies.

[63] Occipitalis: In previous trials, the occipitalis was the third most frequently reported location for pain. In a previous study that explored the follow-the-pain strategy, the occipitalis dose was fixed at 20 units (10 units per side), whereas the highest dose allowed in this muscle in another study was 30 units (15 units per side). The total dose administered to the neck was reduced and thus to ensure that that there would be sufficient “back of the head” dose to ensure efficacy, minimum dose administered to the occipitalis muscle was 30 units (15 units per side); injection sites were standardized and located primarily above the occipital ridge to reduce the risk of neck weakness; optional follow-the-pain dosing with up to an additional 10 units was allowed.

[64] Trapezius: In previous trials, approximately 20%to 30%of patients reported that their headache pain started and/or ended in the trapezius muscles. The follow-the-pain optional injections occurred frequently for this muscle group. Although not a general safety concern,

the incidence of arm (shoulder) pain increased with higher doses; therefore, it was determined that a preferred dosage regimen for the trapezius muscle would be standardized to a minimum dose of 30 units (15 units on each side) and allow optional follow-the-pain injections to a maximum dose of 50 units, if clinically needed.

[65] Masseter: The masseter muscle was not included as a target muscle group for injection in the instant paradigm, as surprisingly injections to the masseter did not aid in treating migraine headaches.

[66] In one aspect of previous trials, the highest total dose per injection cycle evaluated was 260 units and the lowest dose was 105 units (trial one), while the second trial dose groups included 225 units, 150 units, and 75 units. In evaluating a dose response in this trial for tolerability, it was determined that the optimal total dose to maximize efficacy and tolerability was within the range of >150 and <200 units.

[67] In the instant example, subjects were randomized in blinded fashion (1:1) to onabotulinumtoxinA (BOTOX®) (155 units) or placebo, administered as 31 fixed-site, fixed-dose, intramuscular (IM) injections across 7 specific head/neck muscle areas (frontalis, corrugator, procerus, temporalis, occipitalis, cervical paraspinal, and trapezius) (Figure 17): Frontalis† 20 units (2 sites on each side: total 4 sites); Corrugator† 10 units (1 site on each side: total 2 sites) Procerus 5 units (1 site); Occipitalis† 30 units (3 sites on each side: total 6 sites); Temporalis† 40 units (4 sites on each side: total 8 sites); Trapezius† 30 units (3 sites on each side: total 6 sites); Cervical paraspinal muscles† 20 units (2 sites on each side: total 4 sites). Total dose range: 155 units. Each IM injection site = 0.1 mL = 5 U onabotulinumtoxinA (BOTOX®). (†Dose distributed bilaterally.)

[68] Up to an additional 40 units onabotulinumtoxinA or placebo could be administered among 3 muscle groups (occipitalis, temporalis, or trapezius; total of 8 sites) using a protocol-defined, follow-the-pain paradigm (Figure 17). The maximum dose was 195 units at 39 sites. The dose range per injection cycle was 155 units up to 195 units every 12 weeks for 5 cycles.

[69] In practicing this example, medical practitioners were instructed in accordance with the following: dosing/administration: each 100 unit vial of onabotulinumtoxinA (BOTOX®) or placebo was diluted with 2 mL preservative-free normal saline, resulting in a concentration of 5 units /0.1 mL. Doses of 155 units to 195 units or placebo were administered intramuscularly

using a sterile 30-gauge, 0.5-inch needle (with a Luer Lock) as injections of 0.1 mL (5 units) per site. A 1-inch needle was allowed at the physician's discretion in the neck region for patients with thick neck muscles. Guidelines for administering onabotulinumtoxinA were as follows: gloves should be worn while administering treatment; prior to injection, the skin should be cleansed according to standard practice for intramuscular injection (*e.g.* with alcohol); the needle should be inserted into the muscle with the bevel up, at approximately a 45-degree angle; once inserted, the needle hub should be held with 1 hand while the plunger is pulled back slightly with the other hand to prevent torque and blood return, respectively. If blood returns, the needle should be reinserted into the muscle; the plunger should be pushed to administer 0.1 mL (5 units) to each site.

[70] The following is one example of a useful order of injection for administration of botulinum toxin in accordance with the instant disclosure. Anatomic injection sites follow distributions and areas innervated by the first division of the trigeminal nerve and the second cervical nerve.

[71] In an exemplary paradigm, a medical practitioner palpated each muscle (bilaterally, if appropriate) prior to injection to verify muscle delineation and determine the presence of muscle tenderness and/or pain requiring additional treatment. Patients were supine for injections into the corrugator (2 injections, 1 per side), procerus (1 injection, midline), frontalis (4 injections, 2 per side), and temporalis (8 injections, 4 per side), in this sequence (Figure 17). Patients were seated for injections into the occipitalis (6 injections, 3 per side), cervical paraspinal (4 injections, 2 per side), and trapezius (6 injections, 3 per side), in this sequence (Figure 17). If needed, additional injections into the temporalis, occipitalis, and trapezius muscles were allowed, using the optional follow-the-pain paradigm (Figure 17).

[72] Post-administration, patients were observed for 10-15 minutes following treatment and were advised not to rub or massage the affected areas for 24 hours and told that any bumps appearing on the forehead should disappear within approximately 2 hours. Patients were advised that they may need and should use their acute pain medications for breakthrough headaches and to return at 4-week intervals and maintain a headache diary.

[73] Pooled analyses demonstrated statistically significant differences favoring the herein disclosed dose of155 to 195 units over placebo at all time points in the double blind phase

across multiple headache symptom measures, including the pooled primary endpoint of change from baseline in frequency of headache days at 24 weeks: -8.4 onabotulinumtoxinA /-6.6 placebo; $p<0.001$.

[74] Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of embodiments of the present invention provided that the features included in such a combination are not mutually inconsistent.

[75] Example 2 - Botulinum Toxin Type A Therapy for Headache Pain and for a Probable Medication Overuse Headache Disorder

[76] A clinical study was carried out with patients who complained of headache pain and who took frequent acute pain medications such as narcotics and triptans to control the pain. A botulinum toxin (BOTOX®) was administered to the patients at day 0, at day 90 and at day 180. The BOTOX® injections were administered intramuscularly in an average of 20 separate injections to each patient at each of the three injection sessions. The BOTOX® was administered to up to seven different muscles.

[77] From 105 to 260 units of BOTOX® was administered to each patient at each of the three treatment sessions. It was found that the patients experienced a reduction in both (a) the number of headaches experienced by such patients (Figure 1), and; (b) the daily use of acute headache pain medication by these patients (Figure 2). In particular it was found (Figure 3) that a botulinum toxin can reduce use by these patients of narcotic pain medication.

[78] Additionally, it was found that use of a botulinum toxin in patients who were overusing pain alleviation medication resulted in a significant reduction in their use of such medications (*see* Figure 4). It was also found that there was a significant reduction in the intake of triptan medications in overuse patients (Figure 5). Thus, this clinical study surprisingly showed that a botulinum toxin can be used to treat a medication overuse headache disorder (MOU) (*see* Figure 6).

[79] The study also demonstrated (*see* Figure 7) that a botulinum toxin was more effective in patients who were not using a concurrent headache prophylaxis treatment regardless of any medication overuse issue.

[80] Additionally, the same study showed (*see* Figures 8 and 9) that a botulinum toxin was more effective in the patients who were not using a concurrent headache prophylaxis treatment and were overusing medication. This is a discovery in addition to our discovery that a botulinum toxin can be used to treat headache in a patient overusing acute medication, without regard to the fact that the patient is being treated with a botulinum toxin monotherapy or that he or she is being treated for headache with other headache prophylaxis medications.

[81] Furthermore, with regard to acute medication use in patients (not overuse, but any use) the study showed that treatment of headache with a botulinum toxin resulted in a significant decrease in use of narcotics by these patients (*see e.g.* day 210 in Figure 10).

[82] Finally, and significantly the study also showed (*see* Figures 11 and 12) that after treatment with a botulinum toxin there was a greater decrease in the frequency of headache and in the number of days acute analgesic medications were required in the patients who were overusing triptans headache medication at baseline, as compared to the patents who were not overusing triptan medications. This indicates that triptans are more effective to treat headache when used in conjunction with a botulinum toxin. Thus a method for increasing the effectiveness of a triptan to treat a headache can be carried out by using a triptan and a botulinum toxin concurrently to treat a headache.

[83] Clinically, triptan medication overuse appears to actually cause or to exacerbate headache pain, as opposed to the alleviation of headache pain which can result from normal triptan use. Therefore, it was a surprising discovery, as set forth by Figures 11 and 12, to find that administration of a botulinum toxin helps to prevent headaches in a patient population who have headaches, more frequent headaches or exacerbated headaches due to triptan medication overuse. This discovery is demonstrated by study results and patient observations showing that triptan MOU patients needed less triptan medication after botulinum toxin administration.

[84] Example 3 - Botulinum Toxin Type A Therapy for Chronic Headache

[85] This study assessed the potential benefit of BOTOX® in headache prophylaxis in the adult chronic daily headache population. The term chronic daily or chronic near-daily headache has been used to refer to very frequent headaches (16 or more headache days a

month) not related to a structural or systemic illness (Silberstein and Lipton, 2001). The key requirement for entry into the current study was primary headache disorder with ≥ 16 headache days per month by history and confirmed by electronic diary during baseline. Headache disorder could include any combination of episodic/chronic tension-type headaches, migraines with or without aura, and/or migrainous headaches (as defined by IHS criteria [Headache Classification Subcommittee of the IHS, 1988, revised 2004], and/or chronic daily headache as defined by Silberstein and Lipton, 2001).

[86] A study was conducted with a multicenter, double-blind, randomized, placebo-controlled, parallel group of multiple treatments with Botox® for the prophylactic treatment of headaches in a chronic migraine headache population. The overall duration of the study for each patient was 11 months. Patients were screened at Day -60 (baseline period). During this period data were collected daily from the patient regarding specified characteristics of their headache episodes and headache medication use for 30 days using electronic telephone diaries. Following the baseline period, patients returned at Day -30 (Treatment 1) for the placebo run-in period. At this visit, patients meeting the inclusion/exclusion criteria were injected with single-masked placebo, and again recorded specified characteristics of their headache episodes for 30 days using electronic diaries. Treatment 1 injections were in a minimum of 6 muscle areas and 23 to 58 injection sites within these areas, dependent upon the location and severity of pain. The investigator also had the option to inject the masseter if the patient was experiencing pain in that muscle.

[87] After 30 days (at Day 0) patients returned to be randomized for Treatment 2. Prior to randomization, using diary information collected during the placebo run-in period, patients were classified as a placebo responder if they had < 16 headache days or had a ≥ 30% decrease from baseline in the frequency of headache days. All other patients were considered placebo non-responders. Patients within each stratum (responders, non-responders) were randomized to receive either BOTOX® or placebo at Day 0 (Treatment 2).

[88] Patients received additional treatments at Day 90 (Treatment 3) and Day 180 (Treatment 4). Patients returned for follow-up visits at 30-day intervals following each treatment through Day 270. If a patient exited the study at any visit prior to Day 270 (exit), all exit procedures and evaluations were to be completed at that visit. For Treatments 2, 3, and 4, patients were injected with BOTOX® or placebo using the same dose and volume and in the

same muscle areas and sites as in Treatment 1. The schedule of study visits and measurements is shown in Table 2.

[89] The study was randomized and double-blind to minimize investigator and patient bias. Blinding was ensured by the similarity in appearance of the vials of study medication and requiring that an individual at each study center who had no other study involvement reconstituted the study medication and filled the syringes for injection. A placebo-controlled, parallel-group design eliminated possible confounding effects that are inherent in other study designs.

[90] In contrast to the fixed site/fixed dosage treatment approach used in previous clinical studies in the episodic migraine population, physicians participating in this study were allowed to use a more individualized or patient-tailored treatment approach depending on the location of the patient's head pain. Specifically, physicians were given the opportunity to determine the number of injection sites and the dosage within a protocol-specified range to be administered for the specified frontal and posterior muscle areas of the head and neck, depending on the location and severity of a patient's headache. Maximum dose levels allowed in this study also were higher than those used in previous studies due to the addition of injection of larger, posterior pericranial and neck muscles.

[91] Due to the high placebo response rate seen in previous studies, a placebo run-in period was implemented in the present study to stratify patients into 2 groups (placebo responders and non-responders). During the placebo run-in period patients were not informed as to whether they were injected with BOTOX® or placebo. Furthermore, the study protocol was amended to include 3 double-blinded treatment cycles.

[92] Efficacy criteria were as follows. For the primary variable, a difference of 3 headache-free days between BOTOX® and placebo in the mean change from baseline in the frequency of headache-free days per month at Day 180 was considered clinically significant.

- All patients enrolled in this study met at least the following inclusion criteria: male or female, 18 to 65 years old;
- primary headache disorder with ≥ 16 headache days per month by history and confirmed by diary during baseline, which could include any combination of migraines with or without aura, episodic/chronic tension-type headaches, and/or migrainous headaches (as defined by 1988 IHS criteria) (Headache Classification Subcommittee of the IHS, 1988);

- willing and able to give written informed consent;
- stable medical condition;
- stable chronic medications, if any, including non-acute, prophylactic migraine medications, for at least 3 months immediately prior to Day -60;
- willing and able to stay on current medications during the course of the study;
- willing and able to complete the entire course of the study and to comply with study instructions, including diary phone system.

[93] A dose range of units to be injected into each muscle area was defined, except for the occipitalis muscle where the dosage was fixed. The number of injection sites (total of 23 to 58 injection sites) within each specified muscle area (6 to 7 muscle areas) and dose injected (105 U to 260 U) was determined by the physician based on the pain distribution pattern and the severity of pain in the particular muscle area. Patients were to be injected in a minimum of 6 muscle areas, which included the frontal/glabellar, occipitalis, temporalis, semispinalis, splenius capitis, and trapezius muscles, as specified in Table 1 and Figure 13. It was optional to inject the masseter muscle. Patients were to be injected with the same dose and in the same muscle areas and sites for treatments 1, 2, 3, and 4. Whenever possible, treatments for each patient were to be performed by the same physician throughout the study.

[94] Table 1 - Study Medication Dose and Injection Sites

Muscle Area	Number of Units [a]	Bilateral Injection	Total Dose (U)
Frontal/Glabellar	25 - 40	No	25 - 40
Occipitalis	10	Yes	20
Temporalis	10 - 25	Yes	20 - 50
Masseter (optional)	0 - 25	Yes	0 - 50
Trapezius	10 - 30	Yes	20 - 60
Semispinalis	5 - 10	Yes	10 - 20
Splenius capitis	5 - 10	Yes	10 - 20
Total Dose Range			105 - 260

Note: Patients were injected with BOTOX® or placebo in the specified muscles with doses determined by the investigator.

[a] Patients randomized to the placebo group received 0 U of BOTOX®.

[95] Each vial of BOTOX® contained 100 U of botulinum toxin type A, 0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. Each vial of placebo contained 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. The vials were stored in a freezer between -20°C and -5°C before use.

Directions for reconstitution with the diluent, 0.9% sterile saline (without preservatives), for injection were provided in the protocol.

[96] In this study, in contrast to the fixed site/fixed dosage treatment approach used in previous studies, physicians were allowed to use a more individualized or patient-tailored treatment approach. Specifically, the number of injection sites (23 to 58 injection sites) within each specified muscle area (6 to 7 muscle areas) and dose injected (total dose of 105 to 260 U) was determined by the physician based on the patient's usual pain distribution pattern and the severity of pain in the particular muscle area.

[97] During the course of the study, the protocols were amended to include a total of 3 treatment cycles (following the placebo run-in) and the primary endpoint was changed to Day 180 in the placebo non-responder stratum. By the time these amendments were put in place, a significant number of subjects had exited the original study at the planned Day 120 time point. Therefore, enrollment was extended to ensure that at least 90 placebo non-responder patients (45 per treatment group) were available for the Day 180 analysis.

[98] The use of any concurrent medication (*e.g.*, prescription or over-the-counter, including herbal remedies) was recorded on the patient's CRF along with the reason the medication was taken. In addition, medications that the patient had taken for treatment of his or her headaches since 7 days prior to Day -60 were recorded on the appropriate medication CRF. During the study, the patient was to report any use of concomitant medication for headache treatment using the electronic telephone daily diary.

[99] Patients taking concurrent therapies were to maintain a stable dose and dose regimen during the study, particularly with regard to the use of non-acute, prophylactic migraine medications. Medications that were considered necessary for the patient's welfare could be given at the discretion of the investigator. The administration of all medications was to be reported on the CRFs.

[100] Efficacy Measures

[101] Patients recorded start/stop times of headaches, maximum and average severity of headaches, location and type of headache pain, effect on physical activity, presence of aura, presence of associated symptoms of headaches (nausea, vomiting, photo/phonophobia), and headache medications and doses used. The primary efficacy measure was the change from

baseline in the frequency of headache-free days in a 30 day period. The primary visit for determination of efficacy was Day 180, with the evaluation reflecting the prior 30 day period. Baseline for the efficacy measures was defined as the frequency of headache-free days during the first 30 days of the screening period. A difference of 3 headache-free days between BOTOX® and placebo in the mean change from baseline in the frequency of headache-free days per 30-day period at Day 180 was considered clinically significant.

[102] The secondary efficacy measure was the proportion of patients with a decrease from baseline of 50% or more in the frequency of headache days per 30-day period at Day 180. Other efficacy variables included the following:

- proportion of patients with a decrease from baseline of 50% or more in the frequency of headaches per 30-day period;
- frequency of headaches of any severity (per 30-day period);
- frequency of migraine headaches of any severity (per 30-day period);
- proportion of patients with a decrease from baseline of 50% or more in the frequency of migraine headaches per 30-day period;
- proportion of patients with a decrease from baseline of 2 or more migraine headaches per 30-day period;
- moderate to severe migraine headache frequency (per 30-day period);
- patient's global assessment of response to treatment from baseline, as follows:
  - -4 = very marked worsening (about 100% worse or greater)
  - -3 = marked worsening (about 75% worse)
  - -2 = moderate worsening (about 50% worse)
  - -1 = slight worsening (about 25% worse)
  - 0 = unchanged
  - +1 = slight improvement (about 25% improvement)
  - +2 = moderate improvement (about 50% improvement)
  - +3 = marked improvement (about 75% improvement)
  - +4 = clearance of signs and symptoms (about 100% improvement)
- number of days per 30-day period with non-migraine headaches;
- maximum and average headache severity (none, mild, moderate, severe);
- number of days that acute headache medication was used during the study; and
- number of uses (intakes) of acute headache mediation during the study.

[103] Schedule of Assessments

[104] The frequency and timing of study visits and measurements are outlined in Table 2 below.

[105] Table 2 - Schedule of Assessments

	Visit 1 (Baseline Period)	Visit 2 (Placebo Run-In/ Treatment 1)	Visit 3 (Randomi-zation/ Treatment 2)	Visit 4	Visit 5	Visit 6 (Treat-ment 3)	Visit 7	Visit 8	Visit 9 (Treat-ment 4)	Visit 10	Visit 11	Visit 12 (Exit)
	Day –60	Day –30	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 210	Day 240	Day 270
View Video/Obtain Informed Consent	√											
Inclusion/Exclusion Criteria	√	√	√									
Review Medical and Medication History	√	√	√									
Physical Examination	√											√
Vital Signs	√	√	√	√	√	√	√	√	√	√	√	√
Headache Diary Instructions and Review	√	√	√	√	√	√	√	√	√	√	√	
Injection of Study Medication		√	√			√			√			
Patient Global Assessment			√	√	√	√	√	√	√	√	√	√
Pain Diagram	√											√
Headache Count Recall				√	√	√	√	√	√	√	√	√
Beck Depression Inventory	√											
Primary Chronic Headache Assessment									√			
Treatment Assessment Questionnaire						√			√			√
MIDAS	√					√			√			√
Headache-Pain Specific Quality of Life Questionnaire	√		√			√			√			√
Headache Impact Questionnaire	√		√			√			√			√
SF-36 Health Survey	√		√			√			√			√

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	Visit 1 (Baseline Period)	Visit 2 (Placebo Run-In/ Treatment 1)	Visit 3 (Randomi-zation/ Treatment 2)	Visit 4	Visit 5	Visit 6 (Treat-ment 3)	Visit 7	Visit 8	Visit 9 (Treat-ment 4)	Visit 10	Visit 11	Visit 12 (Exit)
Medical Events	√	√	√									
Adverse Events			√	√	√	√	√	√	√	√	√	√
Toxin Neutralizing Antibody Titer Blood Draw	√					√			√			√
CBC/Blood Chemistry	√											√
Urine Pregnancy Test		√	√			√			√			√
Menstrual Cycle Data	√	√	√	√	√	√	√	√	√	√	√	√

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[106] The primary efficacy variable was the change in the frequency of headache-free days from a 30 day baseline period (Day -60 to Day -31). Headache-free days in each 30 day period were determined from data recorded in the telephone electronic diary. Data recorded in the diaries included headache start date and time and headache stop date and time, and the following headache characteristics: usual headache pain (mild, moderate, severe); worst headache pain (mild, moderate, severe); side of the head (unilateral/ bilateral); type of pain (pulsating/throbbing or pressing/squeezing); and effect of physical activity on pain (worse, not worse). It also included headache symptoms: aura (yes or no); interference of activities (yes or no); and other symptoms (nausea, vomiting, sensitivity to light [photophobia], sensitivity to noise [phonophobia]). The diary data also included acute medication taken for the headache (yes or no) and the name and dose of the medication.

[107] Of the 571 patients screened and assessed over the Day -60 to Day -30 baseline period, 355 were enrolled/randomized at Day 0. At the end of the run-in period (Day 0), 279 patients were classified as placebo non-responders and 76 patients as placebo responders. Subsequently patients were randomized within each stratum (placebo no-responders and placebo responders) to receive either BOTOX® or placebo treatment. Within the placebo non-responder stratum, 134 patients received BOTOX® and 145 patients received placebo. Within the placebo responder stratum, 39 patients received BOTOX® and 37 patients received placebo. A total of 76.9% of patients (273/355) completed the study, including 132 patients who completed the original protocol requiring only 1 post-randomization treatment. Of the patients who discontinued early (22.8% [81/355]): 5.1% (18/355) for lack of efficacy, 1.4% (5/355) for adverse events, 0.3% (1/355) for inability to follow study instructions, 1.1% (4/355) for personal reasons, and 2.8% (10/355) were lost to follow up.

[108] There were no significant differences between treatment groups in demographic characteristics. Overall, patients were 19 to 65 years of age (mean, 43.5 years), 84.5% (300/355) were female, and 87.9% (312/355) were Caucasian.

[109] There were no significant differences between treatment groups in baseline characteristics (Table 3).

[110] Table 3 - Baseline Characteristics (As-Treated Population)

Baseline Characteristic	BOTOX® 105 U to 260 U (N=173)	Placebo (N=182)	Total (N=355)	P-value
Years since onset, mean (SD)	14.8 (12.4)	14.2 (12.5)	14.5 (12.4)	0.655 [a]
Age at onset, mean years (SD)	27.5 (12.3)	29.2 (13.6)	28.4 (13.0)	0.301 [a]
Frequency of migraines/probable migraines per 30 day period at baseline	11.2 (6.6)	10.8 (7.9)	11.0 (7.3)	0.274
Use of prophylactic treatment, n (%)	56 (32.4)	71 (39.0)	127 (35.8)	0.192 [b]
Experience menstrual headaches, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	> 0.999 [b]
Baseline MIDAS score, mean (SD)	55.3 (49.6)	59.8 (59.6)	57.6 (55.0)	0.997 [a]
Baseline Beck Depression Inventory score, mean (SD)	7.8 (6.9)	7.9 (6.8)	7.8 (6.9)	0.847 [a]
Mean total dose for the second treatment cycle	190.8 U	NA	NA	NA

SD = standard deviation, NA = not applicable, MIDAS = Migraine Disability Assessment.

[a] P-values for treatment comparisons from the Wilcoxon rank-sum test.

[b] P-values for treatment comparisons from Pearson's chi-square or Fisher's exact tests.

[111] The most common locations where head pain historically started and ended, as reported by patients at baseline, are presented in Table 4.

[112] Table 4 - Location where Headache Pain Historically Starts and Ends Reported at Baseline (Number (%) of Patients)

Location	BOTOX® 105 U to 260 U (N=173)	Placebo (N=182)	Total (N=355)	P-value
Historical Location Where Pain Starts				
Frontal/glabellar	125 (72.7)	140 (76.9)	265 (74.9)	0.357
Temporalis	100 (58.1)	114 (62.6)	214 (60.5)	0.387
Occipitalis	80 (46.5)	85 (46.7)	165 (46.6)	0.971
Historical Location Where Pain Ends				
Frontal/glabellar	123 (71.9)	145 (79.7)	268 (75.9)	0.089
Temporalis	98 (57.3)	113 (62.1)	211 (59.8)	0.360
Occipitalis	97 (56.7)	111 (61.0)	208 (58.9)	0.416

[113] In the analyses of the frequency of headaches per 30 day period, a statistically significant change in the frequency of headaches per 30 day period was observed at Days 30, 60, 150, 180, 210, and 240 for placebo non-responders and at Day 180 for placebo responders (Table 5). Figure 14 presents the mean baseline and the mean changes from baseline in the frequency of headaches per 30-day period for placebo non-responders and placebo responders.

[114] Table 5- Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period for Placebo Non-responders and Placebo Responders

Time Period	Placebo Non-Responders			Placebo Responders		
	BOTOX® (N=134)	Placebo (N=145)	p-value [a]	BOTOX® (N=39)	Placebo (N=37)	p-value [a]
Baseline	13.1 (8.4)	12.8 (9.0)	0.780	15.0 (5.0)	12.3 (4.9)	0.021
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-3.3 (5.0)	-2.0 (4.8)	0.028	-6.7 (6.5)	-5.2 (4.7)	0.705
Day 60	-4.1 (5.5)	-2.6 (5.3)	0.018	-7.4 (5.7)	-5.8 (4.4)	0.855
Day 90	-3.9 (5.6)	-3.2 (5.9)	0.307	-8.0 (6.3)	-5.7 (4.5)	0.534
Treatment 3						
Day 120	-4.6 (5.2)	-3.0 (6.3)	0.118	-7.6 (5.2)	-5.6 (3.3)	0.412
Day 150	-6.3 (6.0)	-3.8 (6.2)	0.039	-8.5 (5.3)	-6.9 (4.6)	0.851
Day 180	-6.1 (5.5)	-3.1 (6.8)	0.013	-9.9 (4.9)	-5.6 (2.8)	0.013

Treatment 4						
Day 210	-6.5 (6.9)	-3.4 (7.0)	0.021	-9.7 (5.8)	-6.6 (4.9)	0.259
Day 240	-7.1 (7.3)	-4.1 (6.5)	0.035	-9.7 (6.1)	-8.2 (4.5)	0.948
Day 270	-7.2 (7.4)	-4.7 (7.3)	0.172	-9.9 (4.7)	-7.4 (5.4)	0.488

Source: Tables 14.2-12.3 and 14.2-12.4.
[a] Between treatment comparison from Wilcoxon rank-sum test.

[115] In the analyses of other protocol-designated efficacy variables, there were statistically significant differences between BOTOX® and placebo in the placebo non-responder and placebo responder groups. Additionally, subgroups of patients were identified for which there was a consistently better response to BOTOX® than to placebo.

[116] Frequency of Headaches, Pooled Population

[117] A statistically significant change in the frequency of headaches per 30-day period was observed at multiple time points (Days 30, 60, 150, 180, 210, and 240) (Table 6). Figure 15 presents the mean baseline and the mean changes from baseline in the frequency of headaches per 30-day period. The analysis of frequency of headaches demonstrated statistically significant differences between BOTOX® and placebo that favored BOTOX®.

[118] Table 6 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period; Pooled Population

Time Period	BOTOX® N = 173	Placebo N = 182	p-value [a]
Baseline	13.5 (7.7)	12.7 (8.3)	0.339
Treatment 1: Placebo (followed by a 30-day run-in period)			
Post Placebo Run-in	-1.9 (4.7)	-1.0 (4.0)	0.336
Treatment 2			
Day 30	-4.1 (5.6)	-2.7 (4.9)	0.021
Day 60	-4.8 (5.7)	-3.2 (5.3)	0.010
Day 90	-4.9 (6.0)	-3.7 (5.7)	0.135
Treatment 3			
Day 120	-5.4 (5.3)	-3.6 (5.8)	0.061
Day 150	-6.9 (5.8)	-4.6 (6.0)	0.033
Day 180	-7.1 (5.6)	-3.7 (6.1)	0.001
Treatment 4			
Day 210	-7.4 (6.7)	-4.2 (6.7)	0.005
Day 240	-7.9 (7.0)	-5.1 (6.3)	0.035
Day 270	-8.0 (6.8)	-5.4 (7.0)	0.080

[a] Between treatment comparison from Wilcoxon rank-sum test.

[119] As seen in Table 6 and Figure 15, the time of the first statistically significant difference between treatment groups in the frequency of headaches per 30-day period was at 30 days after the first treatment following placebo run-in. At this time point, there was a significant difference (p = 0.021) between BOTOX® and placebo demonstrating a rapid onset of effect. The mean changes from baseline were -4.1 for BOTOX® and -2.7 for placebo.

[120] Table 7- Number (Percentage) of Patients with a Decrease from Baseline of 50% or More Headaches per 30-Day Period; Pooled Population

Time Period	BOTOX®	Placebo	p-value [a]
Treatment 1: Placebo (followed by a 30 day run-in period)			
Post Placebo Run-in	23/173 (13.3) [b]	20/182 (11.0)	0.506
Treatment 2			
Day 30	45/172 (26.2)	47/182 (25.8)	0.942
Day 60	60/164 (36.6)	49/166 (29.5)	0.172
Day 90	54/149 (36.2)	49/157 (31.2)	0.352
Treatment 3			
Day 120	33/80 (41.3)	28/82 (34.1)	0.351
Day 150	38/75 (50.7)	33/80 (41.3)	0.240
Day 180	39/72 (54.2)	30/79 (38.0)	0.046
Treatment 4			
Day 210	40/70 (57.1)	28/77 (36.4)	0.012
Day 240	39/70 (55.7)	32/71 (45.1)	0.206
Day 270	40/69 (58.0)	38/69 (55.1)	0.731

[a] Between treatment comparison from Person's chi square test or Fisher's exact test.
[b] Number of patients with response/number of patients evaluated at time period (percentage).

[121] Table 8 presents the mean baseline and the mean changes from baseline in the frequency of headaches per 30-day period for patients who completed 2 and 3 treatment cycles after the placebo run-in period. The 138 patients (69 BOTOX®, 69 placebo) who completed 3 treatment cycles had a sustained response to treatment. Over the 270 day treatment period the response to treatment with BOTOX® generally continued to improve while the response to treatment with placebo remained relatively stable.

[122] Table 8 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period for Patients Who Completed 2 or 3 Injection Cycles After the Placebo Run-in; Pooled Population

	Completed 2 Treatment Cycles After Placebo Run-in			Completed 3 Treatment Cycles After Placebo Run-in		
Time Period	BOTOX® N = 72	Placebo N = 79	p-value [a]	BOTOX® N = 69	Placebo N = 69	p-value [a]
Baseline	14.3 (7.5)	12.8 (8.3)	0.183	14.4 (7.5)	12.6 (8.1)	0.136
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-4.7 (5.3)	-3.4 (5.0)	0.072	-4.7 (5.4)	-3.4 (5.1)	0.098
Day 60	-5.3 (5.3)	-3.5 (5.4)	0.037	-5.3 (5.4)	-3.7 (5.6)	0.091
Day 90	-4.8 (5.6)	-3.5 (5.6)	0.198	-4.7 (5.7)	-3.4 (5.8)	0.229
Treatment 3						
Day 120	-5.8 (5.2)	-3.6 (5.8)	0.023	-5.7 (5.2)	-3.6 (6.0)	0.036
Day 150	-6.8 (5.8)	-4.5 (5.9)	0.042	-6.8 (5.9)	-4.5 (6.1)	0.056
Day 180	-7.1 (5.6)	-3.7 (6.1)	0.001	-7.1 (5.6)	-3.7 (6.3)	0.001
Treatment 4						
Day 210	-7.4 (6.8)	-4.2 (6.7)	0.008	-7.5 (6.7)	-3.9 (6.8)	0.004
Day 240	-7.9 (7.1)	-5.1 (6.3)	0.030	-7.9 (7.0)	-5.0 (6.3)	0.025
Day 270	-8.0 (6.8)	-5.4 (7.0)	0.041	-8.0 (6.8)	-5.4 (7.0)	0.042

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[123] Table 9 presents the mean baseline and the mean changes from baseline in the number of headaches with a duration $\geq$ 4 hours and < 4 hours per 30-day period. Over the 270-day treatment period, in headaches $\geq$ 4 hours in duration, the changes from baseline headache count were significantly greater for BOTOX® than for placebo at every return visit ($p \leq 0.044$; Table 14.5-325). A significant difference between the groups was not seen at any return visit for headaches < 4 hours in duration.

[124] Table 9 - Mean Baseline and Change from Baseline in the Frequency of Headaches for Headaches of a Durations ≥ 4 Hours and < 4 Hours per 30-Day Period

	Headaches of a Duration ≥ 4 Hours			Headaches of a Duration < 4 Hours		
Time Period	BOTOX® N =173	Placebo N = 182	p-value [a]	BOTOX® N = 173	Placebo N = 182	p-value [a]
Baseline	9.6	9.2	0.186	3.9	3.5	0.488
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-2.9	-1.2	0.001	-1.2	-1.5	0.307
Day 60	-3.4	-1.9	0.017	-1.4	-1.3	0.784
Day 90	-3.3	-2.0	0.024	-1.6	-1.7	0.848
Treatment 3						
Day 120	-3.8	-2.0	0.013	-1.6	-1.6	0.867
Day 150	-4.8	-2.8	0.044	-2.0	-1.8	0.906
Day 180	-4.6	-2.2	0.005	-2.5	-1.6	0.134
Treatment 4						
Day 210	-5.1	-2.4	0.003	-2.3	-1.7	0.688
Day 240	-5.1	-3.0	0.016	-2.7	-2.1	0.309
Day 270	-5.5	-3.1	0.013	-2.4	-2.2	0.872

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[125] Efficacy variables for which there were clinically meaningful differences between BOTOX® and placebo in this subpopulation subgroup included: a 50% reduction from baseline in the frequency of headaches per 30-day period; a 30% reduction from baseline in the frequency of headaches per 30-day period; frequency of migraines or probable migraines per 30-day period; and, number of days and number of uses of acute analgesic headache medication per 30-day period.

[126] Table 10 - Baseline Characteristics of Patients Using and Not Using Prophylactic Headache Medications at Baseline; Pooled Population

	Prophylactic Headache Medications at Baseline					
	No			Yes		
Baseline Characteristic	BOTOX® (N=117)	Placebo (N=111)	P-Value	BOTOX® (N=56)	Placebo (N=71)	P-Value
Age, mean years (SD)	42.2 (10.4)	42.5 (11.5)	0.978 [a]	44.4 (8.5)	46.5 (10.3)	0.232 [a]
Sex, n (%)						
Male	11 (9.4)	22 (19.8)	0.025 [b]	11 (19.6)	11 (15.5)	0.540 [b]
Female	106 (90.6)	89 (80.2)		45 (80.4)	60 (84.5)	
Race, n (%)						
Caucasian	102 (87.2)	93 (83.8)	0.466 [b]	52 (92.9)	65 (91.5)	> 0.999 [b]
Non-Caucasian	15 (12.8)	18 (16.2)		4 (7.1)	6 (8.5)	
Years since onset, mean (SD)	15.3 (13.2)	14.3 (12.8)	0.656 [a]	13.8 (10.7)	14.2 (12.1)	0.864 [a]
Age at onset, mean years (SD)	26.2 (12.2)	27.6 (13.1)	0.562 [a]	30.1 (12.1)	31.8 (13.9)	0.407 [a]
Prophylactic headache medications, n (%)						
Beta blockers	NA	NA	NA	16 (28.6)	21 (29.6)	0.901
Calcium channel blockers	NA	NA	NA	9 (16.1)	18 (25.4)	0.204
Anticonvulsants	NA	NA	NA	23 (41.1)	27 (38.0)	0.727
Antidepressants	NA	NA	NA	31 (55.4)	43 (60.6)	0.555
Baseline MIDAS score, mean (SD)	54.0 (44.4)	55.7 (60.3)	0.302 [a]	58.0 (59.7)	66.1 (58.8)	0.264 [a]
Baseline Beck Depression Inventory score, mean (SD)	6.9 (6.6)	7.3 (7.0)	0.945 [a]	9.5 (7.4)	8.6 (6.4)	0.739 [a]

SD = standard deviation, NA = not applicable, NC = not computed.
[a] P-values for treatment comparisons from the Wilcoxon rank-sum test.
[b] P-values for treatment comparisons from Pearson's chi-square or Fisher's exact tests.

[127] The mean baseline and mean changes from baseline to each assessment time point in the frequency of headache days per 30-day period are presented in Table 11 and Figure 16 for the populations of patients using and not using prophylactic headache medications at baseline. The types of prophylactic headache medications used at baseline included beta blockers, calcium

channel blockers, anticonvulsants, and antidepressants (excluding serotonin uptake inhibitors [*e.g.*, PROSAC®] since there is no evidence of any effect in headache for this class).

[128] Table 11 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period by Use of Prophylactic Headache Medications at Baseline; Pooled Population

	Use of Prophylactic Headache Medications at Baseline					
	Yes			No		
Time Period	BOTOX® N = 56	Placebo N = 71	p-value [a]	BOTOX® N = 117	Placebo N = 111	p-value [a]
Baseline	12.4 (7.5)	12.5 (8.6)	0.855	14.1 (7.9)	12.9 (8.2)	0.205
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-2.8 (4.1)	-2.8 (3.7)	0.887	-4.7 (6.1)	-2.5 (5.6)	0.004
Day 60	-3.5 (4.4)	-3.5 (4.6)	0.836	-5.5 (6.1)	-3.0 (5.7)	0.005
Day 90	-3.6 (5.0)	-4.8 (4.9)	0.201	-5.6 (6.3)	-3.0 (6.1)	0.011
Treatment 3						
Day 120	-5.3 (4.3)	-4.0 (4.9)	0.255	-5.5 (6.0)	-3.3 (6.5)	0.072
Day 150	-5.7 (5.1)	-4.7 (5.3)	0.564	-7.8 (6.2)	-4.5 (6.6)	0.032
Day 180	-6.6 (5.0)	-3.9 (4.7)	0.030	-7.5 (6.0)	-3.6 (7.3)	0.007
Treatment 4						
Day 210	-6.7 (5.5)	-4.7 (5.1)	0.138	-7.9 (7.4)	-3.7 (7.9)	0.023
Day 240	-6.6 (6.0)	-5.0 (5.5)	0.279	-8.7 (7.6)	-5.1 (7.1)	0.062
Day 270	-6.9 (6.3)	-5.2 (5.5)	0.369	-8.8 (7.1)	-5.6 (8.1)	0.062

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[129] For patients using antidepressants at baseline (31 BOTOX®, 43 placebo) there were no statistically significant differences between treatment groups at any time point, *except at Day 210* ($p = 0.048$), in the change from baseline in the frequency of headaches per 30-day period. From Day 120 through Day 270, the mean decrease from baseline was greater for BOTOX® by 1.6 to 3.7 headaches per 30-day period. For patients not using antidepressants at baseline, from Day 60 through Day 270, the mean decrease from baseline was greater for BOTOX® by 1.7 to 3.6 headaches per 30-day period. The changes from baseline were significantly greater ($p \leq 0.020$) for BOTOX® at Days 30, 60, and 180.

[130] The percentages of patients at each assessment time point with at least a 50% decrease from baseline in the frequency of headaches per 30-day period (defined as a responder) are

presented in Table 12 for patients using and not using prophylactic headache medications at baseline.

[131] For patients using prophylactic headache medications at baseline, there were no statistically significant differences between BOTOX® and placebo. For patients not using prophylactic headache medications at baseline, from Day 150 through Day 270 at least 50% of BOTOX®-treated patients were responders. The differences between BOTOX® and placebo were statistically significant at Days 150 and 210. At these time points, the response rate for BOTOX® was greater than the response rate for placebo by at least 20%.

[132] Table 12- Number (Percentage) of Patients with a Decrease from Baseline of 50% or More Headaches per 30-Day Period by Use of Prophylactic Headache Medications at Baseline; Pooled Population

	Using Prophylactic Headache Medications at Baseline					
Time Period	Yes			No		
	BOTOX® N = 56	Placebo N = 71	p-value [a]	BOTOX® N = 117	Placebo N = 111	p-value [a]
Treatment 1: Placebo (followed by a 30-day run-in period)						
Post Placebo Run-in	4/56 (7.1%) [b]	7/71 (9.9%)	0.754	19/117 (16.2%)	13/111 (11.7%)	0.325
Treatment 2						
Day 30	10.56 (17.9%)	17/71 (23.9%)	0.405	35/116 (30.2%)	30/111 (27.0%)	0.600
Day 60	15/54 (27.8%)	20/66 (30.3%)	0.762	45/110 (40.9%)	29/100 (29.0%)	0.071
Day 90	15/53 (28.3%)	22/63 (34.9%)	0.446	39/96 (40.6%)	27/94 (28.7%)	0.085
Treatment 3						
Day 120	17/34 (50.0%)	17/39 (43.6%)	0.584	16/46 (34.8%)	11/43 (25.6%)	0.345
Day 150	13/30 (43.3%)	19/38 (50.0%)	0.584	25/45 (55.6%)	14/42 (33.3%)	0.037
Day 180	16/28 (57.1%)	15/38 (39.5%)	0.155	23/44 (52.3%)	15/41 (36.6%)	0.146

Treatment 4						
Day 210	18/29 (62.1%)	17/38 (44.7%)	0.159	22/41 (53.7%)	11/39 (28.2%)	0.021
Day 240	18/29 (62.1%)	17/35 (48.6%)	0.280	21/41 (51.2%)	15/36 (41.7%)	0.402
Day 270	16/29 (55.2%)	19/33 (57.6%)	0.849	24/40 (60.0%)	19/36 (52.8%)	0.526

[a] Between treatment comparison from Person's chi-square test or Fisher's exact test.
[b] Number of patients with response/number of patients evaluated at time period (percentage).

[133] The percentages of patients at each assessment time point with at least a 30% decrease from baseline in the frequency of headaches per 30-day period are presented in Table 13 for patients using and not using prophylactic headache medications at baseline.

[134] For patients using prophylactic headache medications at baseline, there were no statistically significant differences between BOTOX® and placebo. For patients not using prophylactic headache medications at baseline, from Day 30 through Day 270 at least 50% of BOTOX®-treated patients had at least a 30% decrease in the frequency of headaches per 30-day period. The differences between BOTOX® and placebo were statistically significant at Days 30, 60, 150, 180, and 210. At these time points, the response rates for BOTOX® was greater than the response rates for placebo by 16.4 to 26.2%.

[135] Table 13 - Number (Percentage) of Patients with a Decrease from Baseline of 30% or More Headaches per 30-Day Period by Use of Prophylactic Headache Medications at Baseline; Pooled Population

	Use of Prophylactic Headache Medications at Baseline					
Time Period	Yes			No		
	BOTOX®	Placebo	p-value [a]	BOTOX®	Placebo	p-value [a]
Treatment 1: Placebo (followed by a 30-day run-in period)						
Post Placebo Run-in	15/56 (26.8%)	18/71 (25.4%)	0.855	24/117 (20.5%)	29/111 (26.1%)	0.316

Treatment 2						
Day 30	21/56 (37.5%)	28/71 (39.4%)	0.824	61/116 (52.6%)	40/111 (36.0%)	0.012
Day 60	25/54 (46.3%)	28/66 (42.4%)	0.671	62/110 (56.4%)	40/100 (40.0%)	0.018
Day 90	21/53 (39.6%)	36/63 (57.1%)	0.060	59/96 (61.5%)	47/94 (50.0%)	0.112
Treatment 3						
Day 120	20/34 (58.8%)	23/39 (59.0%)	0.990	26/46 (56.5%)	20/43 (46.5%)	0.345
Day 150	18/30 (60.0%)	26/38 (68.4%)	0.471	35/45 (77.8%)	24/42 (57.1%)	0.040
Day 180	20/28 (71.4%)	24/38 (63.2%)	0.481	33/44 (75.0%)	20/41 (48.8%)	0.013
Treatment 4						
Day 210	23/29 (79.3%)	22/38 (57.9%)	0.064	28/41 (68.3%)	18/39 (46.2%)	0.045
Day 240	22/29 (75.9%)	23/35 (65.7%)	0.376	31/41 (75.6%)	22/36 (61.1%)	0.171
Day 270	20/29 (69.0%)	23/33 (69.7%)	0.950	30/40 (75.0%)	23/36 (63.9%)	0.292

[a] Between treatment comparison from Person's chi-square test.

[136] Analyses of the frequency of headaches per 30-day period for patients who were 10 to 20 years and > 20 years since disease onset are given in Table 14. The response to BOTOX® was consistently better than the response to placebo over the entire treatment period for patients with disease onset of 10 to 20 years with a statistically significant difference only at Day 180 and for patients with disease onset of > 20 years with statistically significant differences at Days 30, 60, and 210. Of note is the observation that for the > 20 years subgroup of patients the response to placebo treatment was consistently and considerably lower compared with the response to treatment for the 10 to 20 years subgroup of patients.

[137] Table 14 - Mean (Standard Deviation) Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period by Time From Disease Onset (10 to 20 and > 20 Years); Pooled Population

	Disease Onset 10 to 20 Years			Disease Onset > 20 Years		
Time Period	BOTOX® N = 53	Placebo N = 53	p-value [a]	BOTOX® N = 46	Placebo N = 48	p-value [a]
Baseline	13.2 (7.1)	11.5 (8.1)	0.170	14.1 (7.9)	14.2 (9.5)	0.931
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-3.6 (5.0)	-3.4 (5.1)	0.472	-4.7 (5.0)	-1.9 (4.2)	0.014
Day 60	-4.9 (5.0)	-4.1 (4.9)	0.269	-5.8 (5.8)	-1.8 (5.2)	0.003
Day 90	-4.9 (5.6)	-4.4 (4.9)	0.693	-5.4 (5.4)	-2.8 (6.2)	0.078
Treatment 3						
Day 120	-6.2 (5.8)	-4.5 (5.3)	0.205	-6.1 (4.7)	-2.5 (6.3)	0.107
Day 150	-7.7 (6.2)	-5.7 (5.1)	0.244	-6.3 (5.1)	-3.5 (6.6)	0.146
Day 180	-8.1 (6.4)	-4.8 (5.2)	0.045	-6.1 (4.6)	-2.3 (6.3)	0.055
Treatment 4						
Day 210	-8.3 (6.8)	-6.4 (5.7)	0.256	-6.7 (6.9)	-1.4 (6.9)	0.025
Day 240	-8.2 (6.7)	-6.1 (5.6)	0.278	-8.1 (7.8)	-3.4 (6.7)	0.074
Day 270	-7.4 (6.2)	-6.3 (6.1)	0.481	-8.8 (8.5)	-4.8 (6.9)	0.209

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[138] Analyses of the frequency of headaches per 30-day period by headache-day frequency at baseline (20 to 24 and 25 to 30 headache-days) are summarized in Table 15. The response to BOTOX® was consistently better than the response to placebo over the entire treatment period for patients with a baseline headache-day frequency of 20 to 24 with statistically significant differences at Days 60 and 180, and for patients with a baseline headache-day frequency of 25 to 30 with statistically significant differences at Days 30, 60, and 180. At each time point, the difference between the mean changes for BOTOX® and placebo were greater for patients with a baseline headache-day frequency of 25 to 30.

[139] Table 15 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period for Patients with Headache-Day Frequency of 20 to 24 and 25 to 30 per 30-Day Period at Baseline; Pooled Population

	Headache-Day Frequency of 20 to 24 Per 30-Day Period			Headache-Day Frequency of 25 to 30 Per 30-Day Period		
Time Period	BOTOX® N = 53	Placebo N = 54	p-value [a]	BOTOX® N = 70	Placebo N = 81	p-value [a]
Baseline	16.6 (5.9)	14.8 (6.3)	0.127	11.5 (10.0)	11.5 (10.7)	0.769
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-5.7 (5.1)	-4.2 (5.4)	0.248	-3.5 (6.4)	-1.2 (4.5)	0.014
Day 60	-6.9 (5.7)	-4.7 (5.6)	0.036	-3.9 (6.2)	-1.4 (4.9)	0.015
Day 90	-6.5 (6.1)	-4.6 (5.7)	0.158	-4.0 (6.4)	-2.9 (5.9)	0.318
Treatment 3						
Day 120	-6.9 (5.9)	-4.6 (6.1)	0.166	-4.1 (5.7)	-2.5 (5.9)	0.154
Day 150	-9.0 (6.0)	-6.4 (5.7)	0.137	-6.2 (6.5)	-2.7 (5.6)	0.059
Day 180	-8.9 (6.0)	-5.0 (6.0)	0.038	-6.0 (6.0)	-2.5 (5.8)	0.019
Treatment 4						
Day 210	-9.6 (7.4)	-6.3 (6.1)	0.064	-6.5 (7.6)	-2.4 (6.1)	0.104
Day 240	-10.1 (7.2)	-6.8 (5.5)	0.125	-7.5 (8.6)	-3.1 (6.5)	0.057
Day 270	-10.0 (6.1)	-7.3 (6.1)	0.080	-7.6 (9.1)	-3.3 (7.7)	0.139

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[140] Frequency of Headaches by Baseline Analgesic Acute Headache Medication Overuse

[141] Medication overuse was defined as use of any acute analgesic medication for ≥ 15 days and ≥ 2 days/week. Based on this definition, for patients who did not have overuse of acute analgesic medications at baseline there were no statistically significant differences between BOTOX® and placebo in the changes from baseline in the frequency of headaches per 30-day period at any time point (Table 16). For patients with overuse of acute analgesic medications at baseline, except for Day 90, the difference in the decrease from baseline were significantly greater for BOTOX® than placebo. The mean decreases from baseline were greater for BOTOX® by 2.0 to 5.6 headaches at all time points, except at Day 90 (Table 16).

[142] Table 16 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Headaches per 30-Day Period for Patients with Acute Analgesic Headache Medication Overuse (No, Yes) at Baseline; Pooled Population

	Any Analgesic Overuse for ≥ 15 Days and ≥ 2 Days/Week, No			Any Analgesic Overuse for ≥ 15 Days and ≥ 2 Days/Week, Yes		
Time Period	BOTOX® N = 82	Placebo N = 105	p-value [a]	BOTOX® N = 91	Placebo N = 77	p-value [a]
Baseline	11.7 (6.7)	11.1 (7.5)	0.477	15.2 (8.2)	14.9 (8.9)	0.592
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-3.5 (4.8)	-2.8 (5.0)	0.320	-4.5 (6.1)	-2.5 (4.9)	0.020
Day 60	-4.0 (5.3)	-3.7 (5.4)	0.756	-5.6 (5.9)	-2.6 (5.2)	0.001
Day 90	-4.5 (5.5)	-3.7 (5.8)	0.726	-5.2 (6.4)	-3.7 (5.6)	0.168
Treatment 3						
Day 120	-4.6 (3.9)	-3.6 (6.3)	0.342	-6.2 (6.4)	-3.6 (5.2)	0.044
Day 150	-5.6 (4.7)	-4.9 (5.7)	0.585	-8.2 (6.6)	-4.3 (6.3)	0.018
Day 180	-6.1 (4.7)	-3.8 (6.0)	0.088	-8.1 (6.3)	-3.6 (6.4)	0.003
Treatment 4						
Day 210	-5.5 (5.6)	-4.4 (7.1)	0.495	-9.3 (7.3)	-3.9 (6.2)	0.003
Day 240	-5.7 (4.9)	-5.5 (6.6)	0.885	-10.1 (8.1)	-4.5 (6.1)	0.007
Day 270	-6.3 (4.9)	-5.8 (7.5)	0.800	-9.5 (8.0)	-4.9 (6.4)	0.017

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[143] Type of Headaches

[144] Each headache was classified as migraine (ICHD 1.) or non-migraine (ICHD 2; *e.g.*, tension-type headache). All patients experienced at least 1 migraine during the baseline period, suggesting that all patients may actually have a diagnosis of migraine even though this diagnosis was not recognized by the investigator for all patients. During the study, patients experienced both migraine and non-migraine headaches. The majority of headaches in both treatment groups were classified as migraine (per the ICHD criteria).

[145] Migraine

[146] The mean baseline and mean changes from baseline in the frequency of migraine (ICHD 1.1 or 1.2) or probable migraine (ICHD 1.5.1) headaches per 30-day period are shown in Table 17. At all time points the decreases from baseline were greater for BOTOX® compared with placebo and were significantly greater ($p \leq 0.048$) at Days 120, 180, and 210. At these time points the mean decreases from baseline were greater for BOTOX® by 1.6 to 2.8 headaches.

[147] Table 17 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Frequency of Migraine and Probable Migraine Headaches per 30-Day Period; Pooled Population

Time Period	BOTOX® N = 173	Placebo N = 182	p-value [a]
Baseline	11.2 (6.6)	10.8 (7.9)	0.274
Treatment 1: Placebo (followed by a 30-day run-in period)			
Treatment 2			
Day 30	-3.2 (4.9)	-2.7 (4.4)	0.335
Day 60	-3.9 (5.2)	-3.1 (5.0)	0.134
Day 90	-3.9 (5.6)	-3.5 (5.3)	0.768
Treatment 3			
Day 120	-4.7 (5.0)	-3.1 (5.5)	0.048
Day 150	-5.7 (5.2)	-3.7 (6.0)	0.057
Day 180	-5.8 (5.4)	-3.0 (5.7)	0.002
Treatment 4			
Day 210	-5.9 (5.9)	-3.3 (6.3)	0.018
Day 240	-6.0 (5.6)	-4.2 (5.7)	0.083
Day 270	-6.4 (5.8)	-4.3 (6.5)	0.067

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[148] Non-migraine Headaches

[149] The mean frequency of non-migraine headaches per 30-day period at baseline was 2.3 and 1.8 in the BOTOX® and placebo groups, respectively. There were no statistically significantly differences ($p \geq 0.065$) between BOTOX® and placebo in the changes from baseline in the frequency of non-migraine headaches per 30-day period at all time points *except at Day 90* ($p = 0.034$). At all time points after the run-in period, the mean decreases from baseline were greater for BOTOX® by 0.3 to 1.0 non-migraine headaches. At Day 90 the mean decrease was 1.0 for BOTOX® and 0.2 for placebo.

[150] MOU

[151] There were few statistically significant differences between treatment groups in the use of any acute headache medication (*e.g.* triptans, opioids, etc) during any 30-day treatment period. There were also no statistically significant between-group differences for the individual categories of medication, *i.e.*, ergotamines, triptans, simple analgesics, or anti-emetics. There were *significant differences between* treatment groups for opioids at Day 210 (11.4% [8/70], BOTOX®, 24.7% [19/77] placebo; p = 0.038 and for combination therapies at Day 210 (34.3% [24/70] BOTOX®, 18.2% [14/77] placebo; p = 0.026) and Day 240 (32.9% [23/70] BOTOX®, 18.3% [13/71] placebo; p = 0.048.

[152] The baseline characteristics of patients overusing and not overusing acute analgesic headache medication at baseline at summarized in Table 18. Patients overusing acute analgesic headache medications were significantly older at baseline (mean age, 45.6 versus 41.6 years; p = 0.001), otherwise there were no statistically significant differences between the demographic characteristics of overusers and non-overusers of acute analgesic headache medications at baseline.

[153] Table 18 - Baseline Characteristics of Patients With and Without Analgesic Headache Medication Overuse at Baseline; Pooled Population

	Analgesic Headache Medication Overuse [a] at Baseline		
	Yes	No	
Baseline Characteristic	N = 168	187	P-Value
Age, mean years (SD)	45.6 (9.6)	41.6 (11.0)	0.001 [b]
Sex, n (%)			
Male	32 (19.0)	23 (12.3)	0.079 [c]
Female	136 (81.0)	164 (87.7)	
Race, n (%)			
Caucasian	151 (89.9)	161 (86.1)	0.275 [c]
Non-Caucasian	17 (10.1)	26 (13.9)	
Years since onset, mean (SD)	15.7 (12.6)	13.5 (12.2)	0.075 [b]
Age at onset, mean years (SD)	29.3 (12.4)	27.5 (13.4)	0.153 [b]
Prophylactic headache medications, n (%)	61 (36.3)	66 (35.3)	0.842 [c]
Beta blockers	16 (9.5)	21 (11.2)	0.599 [c]
Calcium channel blockers	14 (8.3)	13 (7.0)	0.624 [c]

	Analgesic Headache Medication Overuse [a] at Baseline		
Anticonvulsants	23 (13.7)	27 (14.4)	0.840 [c]
Antidepressants	38 (22.6)	36 (19.3)	0.435 [c]
Baseline MIDAS score, mean (SD)	54.3 (54.7)	60.6 (55.2)	0.144 [b]
Baseline Beck Depression Inventory score, mean (SD)	7.9 (6.6)	7.8 (7.1)	0.577 [b]

SD = standard deviation.

[a] Overuse = use for ≥ 15 days and ≥ 2 days/week

[b] P-values for treatment comparisons from the Wilcoxon rank-sum test.

[c] P-values for treatment comparisons from Pearson's chi-square or Fisher's exact tests.

[154] At all post-baseline time points, in the BOTOX® compared with the placebo group there was a greater decrease in the number of uses of acute analgesic headache medications, with a statistically significant difference at Days 90 and 210 ($p \leq 0.047$). This also was observed in the analysis of the mean number of days acute analgesic headache medications were used, with statistically significant differences at Days 90, 180, 210, and 240 ($p \leq 0.033$).

[155] Table 19 - Mean (Standard Deviation) at Baseline and Change from Baseline in the Number of Uses and Days of Use of Acute Analgesic Headache Medications per 30-Day Period for Patients Not Using Prophylactic Headache Medications at Baseline; Pooled Population

	Number of Uses of Analgesic Acute Headache Medications			Days with Analgesic Acute Headache Medication Use		
Time Period	BOTOX® N = 117	Placebo N = 111	p-value [a]	BOTOX® N = 117	Placebo N = 111	p-value [a]
Baseline	25.1 (17.7)	21.0 (15.9)	0.058	15.5 (8.4)	13.5 (8.3)	0.069
Treatment 1: Placebo (followed by a 30-day run-in period)						
Treatment 2						
Day 30	-8.7 (13.3)	-5.7 (10.2)	0.096	-4.5 (6.3)	-3.3 (5.9)	0.206
Day 60	-10.3 (14.8)	-6.4 (10.1)	0.076	-5.5 (7.0)	-3.6 (6.6)	0.052
Day 90	-10.3 (14.2)	-6.2 (9.9)	0.047	-5.7 (6.7)	-3.3 (6.8)	0.025
Treatment 3						
Day 120	-10.0 (16.7)	-7.7 (9.0)	> 0.999	-5.7 (6.9)	-4.1 (5.9)	0.427
Day 150	-13.2 (16.5)	-8.7 (10.6)	0.199	-7.9 (6.8)	-5.2 (6.7)	0.098
Day 180	-12.9 (15.5)	-7.9 (11.4)	0.110	-7.8 (6.3)	-4.1 (6.6)	0.015

	Number of Uses of Analgesic Acute Headache Medications			Days with Analgesic Acute Headache Medication Use		
Time Period	BOTOX® N = 117	Placebo N = 111	p-value [a]	BOTOX® N = 117	Placebo N = 111	p-value [a]
Treatment 4						
Day 210	-14.6 (17.3)	-7.4 (11.3)	0.018	-8.5 (7.6)	-4.0 (7.4)	0.011
Day 240	-15.8 (18.1)	-8.5 (9.5)	0.151	-9.3 (8.1)	-4.7 (7.0)	0.033
Day 270	-15.6 (15.9)	-9.2 (11.3)	0.093	-8.8 (7.6)	-5.2 (7.3)	0.086

[a] Between treatment comparison from a Wilcoxon rank-sum test.

[156] Overall, 97.7% (347/355) of patients received acute headache medications while in the study, with similar proportions in each treatment group: 98.3% (170/173) of patients in the BOTOX® group and 97.3% (177/182) in the placebo group.

[157] Overall, 87.6% (311/355) of patients received concomitant medications (other than acute headache medications), with similar proportions in each treatment group: 90.2% (156/173) of patients in the BOTOX® group and 85.2% (155/182) in the placebo group.

[158] A total of 35.8% (127/355) of patients were taking a headache prophylaxis medication during baseline. These included 10.4% (37/355) on beta blockers, 7.6% (27/355 on calcium channel blockers, 14.1% (50/355) on anti-convulsants, and 20.8% (74/355) on anti-depressants. There were no statistically significant differences between the BOTOX progestogens and placebo groups in the number of patients using any of the aforementioned headache prophylactic medications.

[159] During the placebo run-in period (first treatment cycle 1, Day -30 to Day 0) all patients received placebo on Day -30. On Day 0, patients were randomized to receive 3 treatment cycles of intramuscular injections of BOTOX® or placebo. Of the 355 patients enrolled in the study, 173 received 105 U to 260 U BOTOX® and 182 received placebo. The maximum dose of BOTOX® that patients could have received according to the protocol was 260 U per treatment cycle for each of 3 treatment cycles for a total cumulative exposure of 780 U.

[160] Dose

The mean (median) total dose of BOTOX® for the second, third, and fourth treatment cycles was 190.8 U (200 U), 190.9 U (200 U), and 190.5 (200 U), respectively. The mean and median doses of BOTOX® injected into each muscle group for the second, third, and fourth treatment cycles are presented in Table 20. Of note is the observation that the optional injection of the masseter was administered to less than half of the patients in both the BOTOX® and placebo groups.

[161] Table 20 - Mean (Median) Dose of BOTOX® Injected into Each Muscle Group per Treatment

Muscle Injected (Allowable Dose Range)	Treatment Cycle 2 (Day 0)	Treatment Cycle 3 (Day 90)	Treatment Cycle 4 (Day 180)
Frontal/glabellar (25 to 40 U)	38.0 U (40 U)	37.3 U (40 U)	37.1 U (40 U)
Occipitalis (20 U)	19.8 U (20 U)	19.8 U (20 U)	19.7 U (20 U)
Temporalis (20 to 50 U)	42.0 U (40 U)	42.7 U (45 U)	43.7 U (45 U)
Masseter (optional; 0 to 50 U)	8.0 U (0 U)	7.6 U (0 U)	6.5 U (0 U)
Trapezius (20 to 60 U)	47.4 U (60 U)	48.3 U (60 U)	48.4 U (60 U)
Semispinalis (10 to 20 U)	18.2 U (20 U)	18.0 U (20 U)	17.9 U (20 U)
Splenius capitis (10 to 20 U)	18.6 U (20 U)	18.1 U (20 U)	18.1 U (20 U)

Note: During treatment cycle 1 all patients were treated with placebo.

[162] The mean (median) number of sites injected with BOTOX® per muscle group for the first, second, and third injections are presented in Table 21.

[163] Table 21- Mean (Median) Number of Sites BOTOX® Injected per Muscle Group per Treatment Cycle

Muscle Injected (Allowable Dose Range)	Treatment Cycle 2 (Day 0)	Treatment Cycle 3 (Day 90)	Treatment Cycle 4 (Day 180)
Frontal/glabellar (25 to 40 U)	9.5 (9.0)	9.8 (10.0)	9.7 (10.0)
Occipitalis (20 U)	3.0 (2.0)	2.8 (2.0)	2.9 (2.0)
Temporalis (20 to 50 U)	6.5 (6.0)	6.3 (6.0)	6.4 (6.0)
Masseter (optional; 0 to 50 U)	1.3 (0.0)	1.2 (0.0)	1.2 (0.0)
Trapezius (20 to 60 U)	5.9 (6.0)	6.0 (6.0)	6.0 (6.0)
Semispinalis (10 to 20 U)	3.0 (2.0)	2.9 (2.0)	2.9 (2.0)
Splenius capitis (10 to 20 U)	3.1 (2.0)	2.9 (2.0)	3.0 (2.0)

Note: During treatment cycle 1 all patients were treated with placebo.

[164] Significant and consistent efficacy favoring BOTOX® over placebo was observed for the change from baseline in the frequency of headaches per 30-day period. These changes were observed in the placebo non-responder and the placebo responder strata, the pooled data, and in the subgroup of patients with no baseline headache prophylactic treatment. Change in the frequency of headache is a preferred primary endpoint in migraine trials (European Agency for the Evaluation of Medicinal Products, 2003). Recent US FDA approved prophylactic treatment for migraine headache also established efficacy by measuring a change in frequency of headaches (Depakote package insert, 2003).

[165] Significant differences were found between the groups favoring BOTOX® in the percentage of patients with a decrease from baseline of at least 50% or more per 30-day period in the number of headaches at Day 180 (54.2% vs. 38.0%, p = 0.046) and Day 210 (57.1% vs. 36.4%, p = 0.012). In addition, the percentage of patients with a 50% decrease in headaches per 30-day period occurred in more than 50% of patients at Days 150, 180, 210, 240, and 270 in the BOTOX® group, while this level was reached only at Day 270 in the placebo group.

[166] Example 4 - Botulinum Toxin Type A Injection Paradigm for Treating Chronic Migraine

[167] A clinical study was carried out to develop and optimize a dosing and injection paradigm for administration of botulinum toxin, useful in treating migraine, particularly chronic migraine. This study developed a new method and selection of muscles to be injected; minimal, as well as optional maximal, dose and numbers of injection sites per muscle were specified in this study. In this study we used a preferred botulinum toxin formulation (BOTOX®). The injection paradigm herein is particularly useful for treating migraine patients with 15 or more headache days during a 28 day period. In one aspect (double blind phase) the study compared botulinum toxin administration, according to this injection and dosing paradigm, with placebo, as a headache prophylaxis treatment for migraine patients with 15 or more headache days per 4-week period.

[168] We discovered that injection, in a preferred embodiment, of a minimum 31 to maximum 39 injection sites, minimum dose of 155 up to 195 unit maximum administration of botulinum toxin type A (here BOTOX®) injection paradigm detailed below, provided very positive and effective clinical outcomes for patients treated.

[169] In one embodiment of a dosage paradigm utilized in Example 3, administration of 155 units to 195 units (at 31 to 39 injection sites) per treatment cycle was repeated every 12 weeks, up to a maximum of 5 injection cycles. This injection paradigm, in one embodiment, required a minimum dose of 155U using a fixed-site, fixed-dose injection regimen into 31 sites across 7 head/neck muscles. An optional additional dose of botulinum toxin of up to 40U (to up to 8 sites), using a follow-the-pain regimen, provided flexibility in the dosage per muscle for 3 muscles (temporalis, occipitalis and trapezius) to address individual patient needs. In utilizing the optional, additional follow-the-pain regimen portion of this new injection paradigm for these 3 muscles (temporalis, occipitalis and trapezius), the optional and additional botulinum toxin was administered either unilaterally or bilaterally to one or up to three of the specific head/neck muscle areas (temporalis and/or occipitalis and/or trapezius).

[170] Turning to Figure 17, an example of fixed locations to which doses of botulinum toxin was administered to patients (here administered in supine and sitting positions, for example) in accordance with one aspect of an injection paradigm, are depicted. In Figure 17, at each site indicated, 0.1 mL = 5U of Botulinum Toxin Type A was administered. Abbreviations utilized in Figure 17 (under each of the muscles named), mean FSFD=Fixed site, fixed dose; FTP=optional follow-the-pain (locations and amounts of botulinum toxin administered, if utilizing the optional follow-the-pain portion of the injection paradigm, are detailed below).

[171] We have determined that the frontal/glabellar region was the most frequent location where head pain started and ended. We determined that to ensure efficacy, consistency and standardization of treatment, three muscles (frontalis, corrugators and procerus) were selected to be included as part of the 31 fixed site and fixed dosage muscles of the injection paradigm of Example 2. In order to reduce the potential for focal adverse events such as eyelid ptosis, a total dose of 35U was determined to be most advantageous. Furthermore, the exact number and locations for injection to these muscles were specified to ensure optimal tolerability and to specifically minimize eyelid ptosis. Indeed, the specified injection method in these muscles achieved these goals since statistically significant separation from placebo across multiple

headache symptom measures with an overall eyelid ptosis rate for BOTOX® treated patients in the double-blind, placebo controlled phase was found.

[172] In injecting these shallow muscles, the needle was preferably kept superficial to avoid hitting the periosteum. In one aspect, a total of 2 injections was given to the corrugator muscle, one on each side of the forehead (Figure 17, A). The injection site is located approximately 1.5 cm (1 finger breadth) above the medial superior edge of the orbital ridge (bony landmark). The thumb was placed under the corrugator muscle and the injection is done with the needle angled up and away from the eye (towards the forehead), to prevent ptosis of the eyelid. In another aspect, the procerus muscle can have 1 injection site, which is midline on the forehead approximately 1.5 cm above and midline to the medial superior aspect of the orbital ridge (bony landmark) of each eye (Figure 17, B). This injection site is substantially midway between the 2 corrugator injections. In injecting the frontalis, the needle did not need to be directed upward for these injections. A total of 4 injections (2 on the left side and 2 on the right) were given to the frontalis. For the 2 medial injection sites, an imaginary line up from the medial edge of the eyebrow at about 1.5 cm (a finger breadth) from the corrugator injection site is a helpful method for determining needle placement (Figure 17, C). The lateral injection sites were parallel and approximately 1.5 cm lateral of the medial injections sites.

[173] Turning to the temporalis, we determined that the temporalis area was the second most frequent location where head pain started and ended. A fixed-site, fixed-dose regimen for this muscle was utilized in the present injection paradigm. Because this muscle is a very common location of predominant pain for many patients, a minimum dose of 20 units per side (minimum 40 units total) was determined, and up to an additional 10 units total (administered to 1 or both sides in 5 unit increments) to this muscle group was allowed using a follow-the-pain strategy.

[174] The temporal area received a minimum total of 8 injections, 4 to each side (Figure 17, D). In addition, up to 2 additional injections using the optional follow-the-pain paradigm was used. Prior to any injection, the muscles on both sides of the head were palpated for tenderness or pain. Patient clenching of teeth assisted the physician in locating the anterior aspect of the temporalis muscle, which was then palpated. The first injection was made just behind this point, trying to

stay behind the hairline. The second injection was approximately 0.5 cm superior and 1.5 cm posterior to the first injection in the medial aspect of the muscle. The third injection site was parallel and approximately 1.5 cm posterior to the second injection. The fourth fixed-site injection was 1.5 cm below and perpendicular to the second injection, into the medial aspect of the muscle. If additional injections (utilizing the follow-the-pain aspect of this Example 2 injection paradigm) of botulinum toxin were used, additional sites of injection (rather than increasing the injection volume to the fixed 4 sites) were performed.

[175] Turning to the cervical paraspinal muscle group (neck muscles), we determined that headache pain frequently started and/or stopped in the back of the head (either in the occipitalis and/or the neck). Thus it was determined that for the injection paradigm utilized in this Example, injections were given to the upper neck (cervical paraspinal muscles above the occipital ridge) at the base of the skull, rather than to the mid-neck region (to avoid neck pain and neck rigidity), and thus a follow-the-pain injection regimen was not allowed in the neck region, and injections were more superficial rather than inserted deeply into the neck muscles (in one preferred embodiment, the injection needle length and gauge were standardized to 0.5 inch and 30 gauge, respectively) and the total dose injected to the neck region was reduced. Thus the overall dose to the cervical paraspinal muscle group was a fixed-site, fixed-dose of 20U total for this muscle group (10U to each side of the head divided among 4 sites (5 U per site, Figure 17, F)). We determined that this dose is sufficient from an efficacy perspective and this particular neck dose results in less or no neck pain, less or no neck rigidity and decreased the risk of excessive neck muscle weakness, which improved the overall tolerability profile while maintaining efficacy. Beginning on the left side, the cervical paraspinal muscle group injection sites were located by palpating the cervical spine and it was preferable to not to go too deep into the cervical paraspinal and trapezius muscles with the injections (hub of the 0.5 inch needle serves as a relatively accurate “depth” guide). The first injection was administered lateral to the midline, approximately 3-5 centimeters inferior to the occipital protuberance. A second injection was administered on the same side, 1 cm lateral and superior to the first injection (diagonally toward the ear from the first injection). This procedure was repeated symmetrically on the contralateral side, for a total of 4 injections (fixed sites).

[176] Relating to the trapezius, we determined that headache pain frequently started and/or ended in the trapezius muscles. Thus, the dosage regimen for the trapezius muscle was standardized to a minimum dose of 30 U (15U on each side) (to avoid/minimize arm (shoulder) pain), with the option for additional follow-the-pain treatment to a maximum dose of 50U (i.e. an additional 20 units and up to 10 sites overall), if clinically needed.

[177] Accordingly, the superior portions of the trapezius muscles were palpated to identify areas of tenderness and/or pain. Beginning on the left side, the muscle was visually divided into 3 sections. In one embodiment, the first injection to the trapezius was administered in the lateral aspect of the muscle. Moving medially, the mid-portion of the trapezius was administered the second injection, while the third injection was administered medially and superiorly within the third section of the muscle. This procedure was repeated symmetrically on the contralateral side for a total of 6 injections (Figure 17, G.). According to one aspect of the follow-the-pain optional dosing paradigm, an additional 4 injections were, if needed, distributed between the right and left trapezius muscles in the areas identified as having maximal tenderness. The infero-medial portions of the trapezius muscle were avoided to limit the possibility of neck weakness.

[178] Relating to the occipitalis, we determined that the occipitalis was a third most frequent location where headache pain started and ended. In accordance with one aspect of our new injection and dosage paradigm, the minimum dose administered to the occipitalis was 30U at 6 sites for injection into the occipitalis, located primarily above the occipital ridge, which reduced the risk of neck weakness. We also determined that in order to address possible complaints of a predominant pain in the back of the head, additional follow-the-pain dosing was allowed in the occipitalis.

[179] Prior to injecting the occipital area, both the left and right sides were palpated to identify the areas of tenderness and/or pain. To locate the occipitalis injection sites, the external occipital protuberance was palpated. The sites are superior to the supranuchal ridge on either side of this protuberance. In one embedment, three injections were administered to the right and left occipitalis muscles, for a total of 6 injections (Figure 17, E). As an example, the first injection was given just above the occipital protuberance along the supranuchal ridge and approximately 1 cm

left/right (depending on the side) of the external occipital protuberance. The second injection was given approximately 1 cm to the left/right and approximately 1 cm above the first injection. The third injection was given 1 cm medial and 1 cm above the first injection site. According to and in one aspect of an embodiment, the follow-the-pain optional dosing paradigm, an additional 2 injections were, if needed, distributed between the right and left occipitalis muscles (1 injection on each side or 2 injections on 1 side) in the areas that were identified as having maximal tenderness.

[180] In an embodiment of our invention, the masseter muscle was not included as a target muscle group for injection in the instant injection/dosage paradigm utilized. We surprisingly determined that even though some patients had pain in the masseter region as part of their chronic migraine symptoms, injection of botulinum toxin to the masseter muscles was not necessary in order to obtain positive clinical outcomes for the headache patients.

[181] Thus, this paradigm, which utilizes a combination of fixed and follow-the-pain sites for administration of botulinum toxin, provides optimal distribution of botulinum toxin, such as a botulinum toxin type A, based on individual patient symptoms.

[182] Thus, in one embodiment a fixed minimum dose of 155U and fixed number of injection sites (31 sites) divided across 7 specific head and neck muscles (referred to as a fixed-site, fixed-dose regimen) (Table 23) were tested. Interestingly, this protocol also allowed for a modified and outlined follow-the-pain regimen of up to an additional 40U divided across 3 specific muscles: temporalis (up to an additional 10U total in up to an additional 2 sites), occipitalis (up to an additional 10U total in up to an additional 2 sites) and trapezius (up to an additional 20U total in up to an additional 4 sites) (Table 24). As indicated below, the follow-the-pain portion regimen was not required, nor was there a requirement to standardize the use of follow-the-pain from one injection cycle to another injection cycle (toxin administered every 12 weeks).

[183] The overall study was a multicenter, double-blind, randomized, placebo-controlled, parallel-group clinical study with an open-label extension phase, and was conducted for 60 weeks (including a 4-week baseline phase, followed by a 24-week, double-blind treatment phase prior to patients entering a 32-week, open-label extension phase. Patients were randomized/stratified following a 4 week baseline phase, whereby patients meeting the inclusion/exclusion criteria were

assigned a randomization number provided via a central telephone randomization system. Patients were classified as medication overusers ("yes") if they meet 1 or more of these categories.

[184] Table 22- Overuse Criteria

Drug	Criteria for Overuse
Overall: combined across at least two categories among ergotamines, triptans, analgesics (including simple analgesics and combination analgesics as one category) and opioids.	>10 days per month and at least 2 days per week
Ergotamine	≥10 days per month and at least 2 days per week
Triptan	≥10 days per month and at least 2 days per week
Simple Analgesic	≥15 days per month and at least 2 days per week
Opioid	≥10 days per month and at least 2 days per week
Combination analgesic medication	≥10 days per month and at least 2 days per week

[185] Within each stratum, the patient was randomly allocated to receive either botulinum toxin or placebo in a 1:1 ratio. As to the dosage and dose regimen, two (2) treatment sessions in the double-blind phase and three (3) treatment sessions in the open-label extension were conducted. In the double-blind phase, all patients received a minimum dose of 155 U botulinum toxin or placebo administered as 31 fixed-site, fixed-dose injections across seven (7) specific head/neck muscle areas listed in Table 23. In addition, at the medical practitioner's discretion, additional injections of botulinum toxin or placebo were administered unilaterally or bilaterally, using a follow-the-pain paradigm in up to three (3) specific head/neck muscle areas (temporalis, occipitalis, and/or trapezius). According to one embodiment, dosing and number of possible injection sites are described below in table form:

[186] Table 23- Required Dose Using a Fixed-Site, Fixed-Dose Injection

Head/Neck Area	LEFT Number of units per muscle (number of injection sites[a])	RIGHT Number of units per muscle (number of injection sites[a])	TOTAL Number of units per muscle (number of injection sites[a])
Frontalis	10 (2 sites)	10 (2 sites)	20 (4 sites)
Corrugator	5 (1 site)	5 (1 site)	10 (2 sites)
Procerus	-	-	5 (1 site)
Occipitalis	15 (3 sites)	15 (3 sites)	30 (6 sites)
Temporalis	20 (4 sites)	20 (4 sites)	40 (8 sites)
Trapezius	15 (3 sites)	15 (3 sites)	30 (6 sites)
Cervical Paraspinal Muscle Group	10 (2 sites)	10 (2 sites)	20 (4 sites)
Minimum Total	-	-	155 U (31 sites)

[a] 1 injection site = 0.1 mL = 5 U of Botulinum Toxin Type A or 0 U of placebo group

[187] Optional additional injections (*i.e.* in addition to those detailed in Table 23) were not needed to be consistent across treatment visits, with respect to dose or number of injection sites (as they were administered on a case-by-case basis and at the medical practitioner's discretion, but did not exceed the maximum dose allowed (*i.e.* 195 units)). We determined that the medical practitioner takes into account patient-reported usual location of predominant pain, severity of the muscle tenderness while palpating the muscle prior to injection, and the medical practitioner's best judgment on the potential benefit of additional doses in the specified muscles (*e.g.* large muscle size) in determining how many additional units to inject above the fixed minimum amount for a particular muscle region (*e.g.* temporalis and/or occipitalis and /or trapezius) . Thus in one example, the total minimum dose was 155 U with 31 head/neck injections, and the total maximum dose was 195 U with 39 head/neck injections.

[188] Table 24- Optional additional dosing using a follow-the-pain injection paradigm:

Head/Neck Area	LEFT Number of units per muscle (number of injection sites[a])	RIGHT Number of units per muscle (number of injection sites[a])	Location of usual pain or tenderness on palpation	TOTAL Number of units per muscle (number of injection sites[a])
Occipitalis[b]	5 U/site (up to 2 sites)	0	left side	0, 5 or 10 U (0, 1 or 2 sites)
	0	5U/site (up to 2 sites)	right side	
	5 U (1 site)	5 U (1 site)	both sides	
Temporalis[b]	5 U/site (up to 2 sites)	0	left side	0, 5 or 10 U (0, 1 or 2 sites)
	0	5 U/site (up to 2 sites)	right side	
	5 U (1 site)	5 U (1 site)	both sides	
Trapezius[b]	5 U/site (up to 4 sites)	0	left side	0, 5, 10, 15 or 20U (0, 1, 2, 3 or 4 sites)
	5 U/site (up to 3 sites)	5 U (1 site)		
	0	5 U/site (up to 4 sites)	right side	
	5 U (1 site)	5 U/site (up to 3 sites)		
	5 U/site (up to 2 sites)	5 U/site (up to 2 sites)	both sides	
Max. additional				40 U (8 sites)
Max. Total				195 U (39 sites)

[a] 1 injection site = 0.1 mL = 5 U of Botulinum Toxin Type A or 0 U of placebo group

[b] Maximum additional dose distributed unilaterally or bilaterally is as follows: Occipitalis = 10 U, Temporalis = 10 U, Trapezius = 20 U

[189] During the baseline phase of this example (Week -4 to Day 0) the patient had at least 15 headache days and at least 4 headache episodes of any type each with a minimum duration of 4 hours. At least 50% of these headache episodes were classified as migraine (ICHD-II 1.1 or 1.2), or probable migraine (ICHD-II 1.6). After the 4-week baseline phase, prospective patients returned to the investigators office to qualify for entry into the 24-week double-blind treatment phase.

Women of childbearing potential had a negative urine pregnancy test prior to entry into the 4-week baseline phase and also prior to the first injection of study medication at Day 0.

[190] Accordingly and as one example, a combined fixed site and follow-the pain paradigm of botulinum toxin dosing and administration sites, having a minimum number of head, neck, shoulder areas to be administered a minimum amount of botulinum toxin, along with a subset of those head, neck, shoulder areas to which additional botulinum toxin can be administered (up to a stated maximum dosage, such as a maximum dosage enumerated in a package insert or prescribing information is disclosed.

Claims

We claim:

1. A method for prophylactically treating a headache in a patient with chronic migraine headaches, the method essentially consisting of:

local administration of a botulinum neurotoxin to the frontalis, corrugator, procereus, occipitalis, temporalis, trapezius and cervical paraspinal muscles of the patient that suffers from the migraine headache;

wherein the botulinum neurotoxin is administered, to the frontalis at about twenty units divided among four sites of injection; to the corrugator at about ten units divided among two sites of injection; to the procerus at about five units to one site of injection; to the occipitalis at about thirty units divided among six sites of injection to about forty units divided among eight sites of injection; to the temporalis at about forty units divided among eight sites of injection up to fifty units divided among ten sites of injection; to the trapezius at about thirty units divided among six sites of injection up to about fifty units divided among ten sites of injection and to the cervical paraspinal muscles at about twenty units divided among four sites of injection;

wherein the botulinum neurotoxin is injected at 31 to 39 injection sites.

2. The method of claim 1 wherein the total amount of botulinum neurotoxin administered is from about 155 units to about 195 units of onabotulinumtoxinA.

3. The method of claim 1 wherein the botulinum neurotoxin is type B.

4. The method of claim 1 wherein the botulinum neurotoxin is type E.

5. The method of claim 1 wherein the botulinum neurotoxin is type A.