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(54) **Title**: LONG LASTING EFFECT OF NEW BOTULINUM TOXIN FORMULATIONS

(57) **Abstract**: The invention relates to the use of an animal-protein-free botulinum toxin composition to treat a disease, disorder or condition in a patient in need thereof whereby the animal-protein-free botulinum toxin composition exhibits a longer lasting effect in the patient compared to an animal-protein-containing botulinum toxin composition.

TITLE OF THE INVENTION

LONG LASTING EFFECT OF NEW BOTULINUM TOXIN FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 61/915,476, filed December 12, 2013, hereby incorporated entirely by reference.

BACKGROUND OF THE INVENTION

Pioneered in the mid-late 1980s, chemical denervation of the corrugator and/or procerus muscles with botulinum toxin A (BoNT/A) met many of the criteria of an ideal cosmetic technique for the treatment of glabellar frown lines. When carried out by experienced personnel, BoNT/A injection rapidly and reversibly ameliorates or even eliminates glabellar lines, with virtually no significant adverse effect (Becker-Wegerich P, et al., Clin Exp Dermatol, 2001 Oct; 26(7):619-30; Letessier S., J Dermatol Treat, 1999; 10(1):31-6 and Alam M, et al., Arch Dermatol, 2002 Sep; 138(9):1180-5).

In 2002, a decade after the first published report on the use of BoNT/A in the treatment of glabellar frown lines (Carruthers JDA, et al. J Dermatol Surg Oncol, 1992 Jan; 18(1):17-21) the acknowledged efficacy and tolerability of BoNT/A's effect on glabellar lines was finally confirmed in two identical, large, multicenter, placebo controlled trials (Carruthers JA, et al., J Am Acad Dermatol, 2002 Jun; 46(6):840-9 and Carruthers J, et al., Journal of Plastic and Reconstructive Surgery 2003). Since then, BoNT/A has been used widely in a variety of manners to temporarily treat glabellar lines and other hyperfunctional facial lines, including horizontal forehead lines ('thinker's wrinkles') and lateral orbital lines ('crow's feet').

Currently commercially available BoNT/A all contain animal proteins such as albumin. Further commercially available BoNT/A compositions such as BOTOX® have a duration of effect of approximately 3 months for treating conditions such as crow's feet lines or glabellar lines.

Accordingly, there is a need in the art for a new type of BoNT composition that is effective and safe with a duration effect longer than commercially available BoNT

compositions (e.g. BOTOX®, DYSPORT®, or XEOMIN®). The present invention fulfills this need.

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description of preferred embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

Figure 1 is an image showing the study design and schedule of assessments.

Figure 2 is an image showing the injection sites. The glabellar lines received a single session of either MT10109L or ona-BoN/T. The 0.5 mL (20 U) total injection volume was divided into five symmetrical intramuscular injections: 0.1 mL (4 U) in the procerus muscle, 0.1mL (4 U) in each medial corrugator supercilli muscles, and 0.1mL (4 U) in the middle of each corrugator supercilli muscles.

Figure 3, comprising Figures 3A and 3B, is a series of images showing responder rate at maximum frown by live assessment (Figure 3A) PP set and (Figure 3B) FAS set.

Figure 4, comprising Figures 4A and 4B, is a series of images showing (Figure 4A) responder rate by subject's assessment (PP set) and (Figure 4B) subject's satisfaction rate (PP set).

Figure 5 is a graph demonstrating the difference in proportion of responders as indicated by investigator assessment rating of glabellar line severity at maximum frown at day 30 for various dosages of lyophilized MT10109 (10U, 20U, and 30U) compared to 20U Botox® (full analysis set). Abbreviations. CI=confidence interval; vs = versus. A responder was defined as having a glabellar line severity rating of none (0) or mile (1) at the corresponding post-baseline visit. The analysis was on inputed data using multiple imputation methodology. A Mantel-Haenszel chi-square test was used to compare treatments 2 by 2 and estimate the differences between the two treatments.

Figure 6 is a graph depicting the percent of responders as indicated by investigator assessment rating of glabellar line severity at all visits (full analysis set).

Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a severity of none (0) or mild (1) at the corresponding post-baseline visit.

Figure 7 is a graph depicting the percent of responders as indicated by subject's self-assessment of glabellar line improvement (full analysis set). Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least +2 (moderate improvement, i.e., about 50%) on the 9-point scale.

Figure 8 is a graph depicting the percent of responders as indicated by subject's self-assessment of satisfaction with the effect of treatment (full analysis set). Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least 6 (satisfied) on the 7-point scale.

Figure 9 is a set of graphs depicting the results of experiments. The data includes percent responding as a function of days post treatment as indicated by investigator assessment at max frown (top left), investigator assessment at rest (middle left), independent reader at frown (top right), independent reader at rest (middle right), subject global assessment (bottom left), and subject satisfaction (bottom right).

Figure 10 is a set of graphs depicting the results of experiments. The data includes the percent responding as indicated by investigator at max frown. The top graph displays the collective data. The graphs at middle left and bottom left represent the data from site 1, while the graphs at middle right and bottom right represent the data from site 2.

DETAILED DESCRIPTION

The invention relates to the use of an animal-protein-free botulinum toxin composition to treat a disease, disorder or condition in a patient in need thereof whereby the animal-protein-free botulinum toxin composition exhibits a longer lasting effect in the patient compared to an animal-protein-containing botulinum toxin composition.

In at least one embodiment, the animal-protein-free botulinum toxin composition is formulated in a liquid form. In certain embodiments the liquid formulation of an animal-protein-free botulinum toxin composition is the formulation disclosed in US

20100291136, which is incorporated herein by reference in its entirety. In certain embodiments, the liquid formulation of an animal-protein-free botulinum toxin composition allows for the activity of botulinum toxin to be stably maintained under a refrigerated or high temperature condition with the use of neither animal-derived protein, such as albumin or gelatin, as a stabilizer for botulinum toxin nor polar or acidic amino acids such as glutamine, glutamic acid, asparagine or aspartic acid.

In at least one embodiment, the animal-protein-free botulinum toxin composition is formulated in a lyophilized form. In certain embodiments the lyophilized preparation of an animal-protein-free botulinum toxin composition is the formulation disclosed in PCT/KR2012/002418, which is incorporated herein by reference in its entirety. In certain embodiments, the lyophilized formulation of an animal-protein-free botulinum toxin composition allows for maintaining botulinum toxin activity and achieving remarkably superior long-term stability even under high-temperature conditions which might occur during storage, transportation, or use of botulinum toxin.

In certain embodiments, the efficacy of the animal-protein-free botulinum toxin composition (e.g., a liquid formulation or a lyophilized form) persists longer in the patient compared to an animal-protein-containing botulinum toxin composition. In certain embodiments, the administration of the animal-protein-free botulinum toxin composition (e.g., a liquid formulation or a lyophilized form) allows for larger interval time between administrations of the botulinum toxin composition compared to the interval time when using an animal-protein-containing botulinum toxin administered at the same or comparable dose and at the same or comparable sites.

In certain embodiments, the invention provides a treatment regimen that includes using an animal-protein-free botulinum toxin composition wherein the botulinum toxin composition is administered to a patient in need thereof at a lower dose compared to the dose used with an animal-protein-containing botulinum toxin composition.

In certain embodiments, the invention provides a treatment regimen that includes using an animal-protein-free botulinum toxin composition wherein the botulinum toxin composition is administered to a patient in need thereof at a greater time interval between administrations compared to the time interval used with an animal-protein-containing botulinum toxin composition (e.g. commercially available botulinum toxin type A

includes BOTOX®, DYSPORT®, and XEOMIN®; commercially available botulinum toxin type B includes MyoBloc®).

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

"About," as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20%, ±10%, ±5%, ±1%, or ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

A disease or disorder is "alleviated" if the severity of a symptom of the disease or disorder, the frequency with which such a symptom is experienced by a patient, or both, is reduced.

As used herein, the term "animal-protein-free botulinum toxin composition" refers to a botulinum toxin composition that does not contain blood derived, blood pooled or other animal derived products (e.g. does not contain albumin). In certain embodiments, the animal-protein-free botulinum toxin composition is free of human serum albumin or recombinant human albumin.

As used herein, the term "animal-protein-containing botulinum toxin composition" refers to a botulinum toxin composition that contains a blood derived, blood pooled or other animal derived product (e.g. contains albumin). In certain embodiments, animal-protein-containing botulinum toxin composition contains human serum albumin or recombinant human albumin.

"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.

The terms "patient," "subject," "individual," and the like are used interchangeably herein, and refer to any animal, or cells thereof whether *in vitro* or *in situ*, amenable to the methods described herein. In certain non-limiting embodiments, the patient, subject or individual is a human.

As used herein, the term "composition" or "pharmaceutical composition" refers to a mixture of at least one compound of the invention with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism.

As used herein, the terms "effective amount," "pharmaceutically effective amount" and "therapeutically effective amount" refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

As used herein, the term "efficacy" refers to the maximal effect (E_{max}) achieved within an assay.

"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.

"Long lasting" or "longer lasting" or "greater duration" refers to the longer duration of efficacy of an animal-protein-free botulinum toxin composition when compared to an animal-protein-containing botulinum toxin composition that is dosed at the same or comparable amount and administered in the same manner (e.g. by injection) to the same or comparable location(s).

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

"Pharmaceutically acceptable" refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability. "Pharmaceutically acceptable carrier" refers to a medium that does not interfere with the effectiveness of the biological activity of the active ingredient(s) and is not toxic to the host to which it is administered.

A "therapeutic" treatment is a treatment administered to a subject who exhibits signs or symptoms of pathology, for the purpose of diminishing or eliminating those signs or symptoms.

As used herein, the term "treatment" or "treating" is defined as the application or administration of a therapeutic agent, i.e., a compound of the invention (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (e.g., for diagnosis or ex vivo applications), who has a condition contemplated herein, a symptom of a condition contemplated herein or the potential to develop a condition contemplated herein, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a condition contemplated herein, the symptoms of a condition contemplated herein or the potential to develop a condition contemplated herein. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual

numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

Description

The present invention is based on the discovery that an animal-protein-free botulinum toxin composition exhibited an improved outcome in a recipient patient compared to an otherwise identical patient receiving an animal-protein-containing botulinum toxin composition when the patient was evaluated 16 weeks after the administration of the botulinum toxin composition. That is, the animal-protein-free botulinum toxin composition exhibits a longer lasting effectiveness compared to an animal-protein-containing botulinum toxin composition.

Liquid Animal-Protein-Free Formulation

Compositions useful in the invention include an animal-protein-free botulinum toxin composition. In certain embodiments, the animal-protein-free botulinum toxin composition is in a liquid formulation.

In certain embodiments, the liquid pharmaceutical composition used in the present invention comprises botulinum toxin, polysorbate 20, and methionine.

In certain embodiments, the liquid pharmaceutical composition used in the present invention comprises botulinum toxin, polysorbate 20, methionine and isoleucine.

In certain embodiments, the liquid pharmaceutical composition comprises a botulinum toxin, polysorbate 20 and methionine and optionally isoleucine.

With the employment of polysorbate 20, methionine and optionally isoleucine, instead of an animal-derived protein such as albumin or gelatin, as stabilizers for botulinum toxin, the liquid pharmaceutical composition used in the present invention excludes the potential risk of infecting the recipient with serum-derived pathogens or microorganisms and is thus safe for ingestion into the body. In addition, the use of the stabilizers polysorbate 20, methionine and optionally isoleucine allows for higher stability to botulinum toxin composition at around 25°C to about 37°C. Thus, in terms of the storage stability of botulinum toxin composition at 25°C to about 37°C, the liquid pharmaceutical composition is very useful for storing botulinum toxin composition under

an emergency condition such as an environment without maintaining low temperature, thus being superior to conventional liquid pharmaceutical compositions employing either detergents or amino acids.

In certain embodiments, the methionine is present in an amount of about 0.5 to 100 μmol per 100 units of botulinum toxin, and preferably ranges in concentration from about 0.5 to 100 mM and more preferably from about 25 to about 75 mM. In another embodiment, the methionine ranges in concentration from about 0.5 mM to about 100 mM.

A methionine content less than 0.5 μmol per 100 units of botulinum toxin cannot guarantee the stabilization of the botulinum toxin to a desirable level upon long-term storage at room temperature. On the other hand, when methionine is used in an amount exceeding 100 μmol per 100 units of botulinum toxin, the excess increment may not promise an additional stabilization effect in addition to incurring an economic disadvantage. In the liquid pharmaceutical composition used in the present invention, methionine properly ranges in concentration from 0.5 to 100 mM when the botulinum toxin has a concentration of 100 units/mL. Its proper concentration is adjusted to about 25mM to about 75 mM in consideration of the concentration range of polysorbate 20. When the concentration of methionine is below 25 mM in the liquid pharmaceutical composition used inf the present invention, its long-term stabilization effect on botulinum toxin at room temperature does not reach the desirable level, which is obtainable in the proper concentration range of botulinum toxin. On the other hand, a methionine concentration exceeding 75 mM does not provide any additional effect.

In certain embodiments, polysorbate 20 is present in an amount of 0.01 to 50 mg per 100 units of botulinum toxin and preferably ranges in concentration from 0.01 to 50 mg/mL and more preferably form 0.1 to 2.5 mg/mL.

Polysorbates are a class of emulsifiers used in some pharmaceuticals and in food preparation. They are often used in cosmetics to dissolve essential oils into water-based (oil-in-water) products. There are many kinds of polysorbates that are classified by a number referring to the total number of oxyethylene groups, such as polysorbate 20, 40, 60 and 80. In certain embodiments, the liquid pharmaceutical composition used in the

present invention employs polysorbate 20 (commercially available as brand name Tween 20) as a stabilizer for botulinum toxin.

If the liquid pharmaceutical composition used in certain embodiments of the present invention contains polysorbate 20 in an amount less than 0.01 mg per 100 units of botulinum toxin, its long-term stabilization effect on botulinum toxin at room temperature does not reach a desirable level. On the other hand, a polysorbate 20 concentration exceeding 50 mg/mL does not provide any additional effect in addition to incurring an economic disadvantage. At a concentration of 100 units/mL of botulinum toxin in the liquid pharmaceutical composition used in certain embodiments of the present invention, polysorbate 20 is properly present in an amount of about 0.01mg/mL to about 50 mg/mL and preferably in an amount of about 0.1 mg/mL to about 2.5 mg/mL when the methionine concentration is taken into consideration. When the concentration of polysorbate 20 in the liquid pharmaceutical composition used in certain embodiments of the present invention is less than 0.1 mg/mL, its long-term stabilization effect on botulinum toxin at room temperature does not reach a desired level, which is obtainable by the target concentration of polysorbate 20. On the other hand, a polysorbate 20 concentration exceeding 2.5 mg/mL does not provide any additional effect.

The botulinum toxin, a constituent of the liquid pharmaceutical composition used in certain embodiments of the present invention, may be one selected from among serotypes A, B, C, D, E, F and G. The term botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium Clostridium botulinum and, to date, seven immunologically distinct neurotoxins serotypes have been identified. These have been given the designations A, B, C, D, E, F and G, which differ one from the other in their effects on target animals, and paralysis extent and duration. All serotypes of botulinum toxin are known to act as a neurotoxin by inhibiting the neurotransmitter acetylcholine at neuromuscular junctions.

The botulinum toxin of the liquid pharmaceutical composition used in certain embodiments of the present invention may be in a non-complex form or in a complex form with another protein. Botulinum toxin serotype A, B, C, D, E, F or G alone, synthesized by Clostridium botulinum, itself has a molecular weight of approximately 150 kDa. When expressed in Clostridium botulinum, the botulinum toxin forms various

complexes with hemagglutinin proteins and non-hemagglutinin proteins which aid and protect the activity thereof. Naturally occurring botulinum type A complexes have a molecular weight of approximately 900 kDa, 500 kDa or 300 kDa. Molecular weights are measured to be approximately 500 kDa for botulinum toxin type B complexes and type C complexes, approximately 300 kDa or 500 kDa for type D complexes, and approximately 300 kDa for type E and type F complexes.

In certain embodiments, the concentration of the botulinum toxin in the liquid pharmaceutical composition preferably ranges from 50 to 5,000 units/mL depending on the general use thereof.

In certain embodiments, the liquid pharmaceutical composition using in the present invention has a pH of about 5.5 to 7.0. In certain embodiments, when the liquid pharmaceutical composition used in the present invention is adjusted to a pH of about 5.5 to about 7.0, botulinum toxin is stably maintained at room temperature (particularly 40°C) for a long period of time.

The liquid pharmaceutical composition can be readily prepared because it employs a detergent and an amino acid(s) without a lyophilization process.

Lyophilized Animal-Protein-Free Botulinum Toxin Formulation

Compositions useful in the invention include an animal-protein-free botulinum toxin composition. In certain embodiments, the animal-protein-free botulinum toxin composition is a lyophilized preparation of botulinum toxin. For example, the lyophilized preparation of botulinum toxin composition useful in the invention does not contain a protein stabilizer derived from an animal.

In certain embodiments, the present invention provides a lyophilized preparation of a botulinum toxin composition comprising: 1) botulinum toxin; 2) polysorbate; 3) methionine; and 4) one or more components selected from a group consisting of sugar, sugar alcohol, an ionic compound, and a combination thereof.

In certain embodiments, when the botulinum toxin composition is formed as a lyophilized preparation, the component(s) play(s) a role in maintaining the activity of the botulinum toxin composition while facilitating stabilization at temperatures greater than room temperature. At the time of lyophilization, preparations containing 1) botulinum

toxin; 2) polysorbate; and 3) methionine exhibit reduced stability, and when they are formulated as a liquid preparation they experience reduced stability at temperatures greater than room temperature; however, the lyophilized preparation of botulinum toxin composition used in certain embodiments of the present invention not only maintains the activity of the botulinum toxin composition at temperatures greater than room temperature, but also is excellent relative to storage stability over long periods.

The botulinum toxin may be derived from Clostridium botulinum. The botulinum toxin may be separated and refined from these strains by known methods, or else a commercially available product may be used.

The botulinum toxin may be randomly selected from a group consisting of botulinum Serotypes A, B, C, D, E F and G.

The botulinum toxin present in the lyophilized preparation may be in forms containing and not containing proteins in complexes. The activity of the botulinum toxin is unaffected whether or not the protein is in a complex. In the lyophilized preparation of botulinum toxin composition used in certain embodiments of the present invention, polysorbate, which is one of the stabilizers of the botulinum toxin, is a non-ionic surfactant, and is primarily used as an emulsifier in the pharmaceutical or food industries. As polysorbate types, there are polysorbate 20, 40, 60, 80 or 100, based on the total number of oxyethylene groups. For the lyophilized preparation of botulinum toxin composition used in certain embodiments of the present invention, it is acceptable to use any from among these. The polysorbate may be present at an amount of about 0.01 to about 2 mg per 100 units of the botulinum toxin. If polysorbate is present within this range, then the activity of the botulinum toxin can be maintained even at temperatures greater than room temperature, and long-term storage stability can be maintained.

In certain embodiments, methionine, which is one of the stabilizers, may also be used as a substitute for animal proteins such as albumin or gelatin, as the stabilizer for the botulinum toxin. The methionine may be present at an amount of about 0.01 to 10 mg per 100 units of the botulinum toxin. If methionine is comprised within this range, then the activity of the botulinum toxin composition can be maintained even at temperatures greater than room temperature, and long-term storage stability can be maintained.

Different from existing liquid preparations, the lyophilized preparation of botulinum toxin composition used in certain embodiments of the present invention further comprises at least one from among sugar, sugar alcohol or an ionic compound, as an additional component aside from methionine and polysorbate. Sugar is known to protect the denaturation of the macromolecule. As a sugar that may be used in the lyophilized preparation used in certain embodiments of the present invention, trehalose, sucrose, maltose, fructose, lapinose, lactose or glucose may be used; however, the use thereof is not limited to these types. The sugar may be at an amount of about 0.1 to 50 mg per 100 units of the botulinum toxin. If sugar is present within this range, then the activity of the botulinum toxin composition can be maintained even at temperatures greater than room temperature, and long-term storage stability can be maintained.

Sugar alcohol is known to stabilize the macromolecule under lyophilization conditions, and to usefully prevent denaturation. As a sugar alcohol that may be used in the lyophilized preparation used in certain embodiments of the present invention, cylodextrin, mannitol, sorbitol, glycerol, xylitol or inositol, etc. may be used. The sugar alcohol may be at an amount of about 0.1 to 50 mg per 100 units of the botulinum toxin. If sugar alcohol is present within this range, then the activity of the botulinum toxin composition can be maintained even at temperatures greater than room temperature, and long-term storage stability can be maintained.

In certain embodiments, "ionic compound" refers to a salt, buffer, etc. The ionic compound works with the macromolecule through specific or non-specific binding. Salt can increase thermal stability, increase solubility and decrease the degree of aggregation. However, caution is required with high concentrations of salt due to the observed tendency for protein denaturation. As the ionic compound, sodium chloride, sodium phosphate, ammonium phosphate, magnesium sulfate, sodium acetate, sodium lactate, sodium succinate, sodium propionate or potassium phosphate may be used; however, the use thereof is not limited to these types. The ionic compound may be present at an amount of about 0.1 to 10 mg per 100 units of the botulinum toxin. If the ionic compound is present within this range, then the activity of the botulinum toxin composition can be maintained even at temperatures greater than room temperature, and long-term storage stability can be maintained.

In certain embodiments, the lyophilized preparation of botulinum toxin composition used in the present invention is manufactured from the culture of Clostridium botulinum that has been cultured in a specific medium, although this is not limited. The botulinum toxin complex is purified through a series of acid precipitations as a crystalline complex composed of active high molecular weight toxin protein and related Hemagglutinin protein. The crystalline complex is dissolved in a solution containing salt and stabilizer, and the lyophilized preparation of botulinum toxin composition is produced by undergoing a freeze drying process.

Method

The invention relates to the use of an animal-protein-free botulinum toxin composition to treat a disease, disorder or condition in a patient in need thereof whereby the animal-protein-free botulinum toxin composition exhibits a longer lasting effect in the patient compared to an animal-protein-containing botulinum toxin composition. For example, it was observed that an animal-protein-free botulinum toxin composition exhibited a greater improvement on the therapeutic outcome in a patient compared to the outcome of the patient receiving an animal-protein-containing botulinum toxin composition.

In certain embodiments, the efficacy of the animal-protein-free botulinum toxin composition (e.g., a liquid formulation or a lyophilized form) persists longer in the patient compared to an animal-protein-containing botulinum toxin composition. In certain embodiments, the administration of the animal-protein-free botulinum toxin composition (e.g., a liquid formulation or a lyophilized form) allows for larger interval time between administrations of the botulinum toxin composition compared to the interval time when using an animal-protein-containing botulinum toxin administered at the same or comparable dose and at the same or comparable sites.

In certain embodiments, the invention provides a treatment regimen that includes using an animal-protein-free botulinum toxin composition wherein the botulinum toxin composition is administered to a patient in need thereof at a lower dose compared to the dose used with an animal-protein-containing botulinum toxin composition.

In certain embodiments, the invention provides a method for treating a condition in a patient in need thereof, the method comprising the step of locally administering a therapeutically effective amount of an animal-protein-free botulinum toxin composition, whereby at least one symptom of the condition is thereby effectively alleviated for a period of time longer than that of an animal-protein-containing botulinum toxin composition.

In certain embodiments, the invention provides a treatment regimen that includes using an animal-protein-free botulinum toxin composition wherein the botulinum toxin composition is administered to a patient in need thereof at a greater time interval between administrations compared to the time interval used with an animal-protein-containing botulinum toxin composition.

In certain embodiments, the invention provides a method for treating a condition in a patient in need thereof, the method comprising the step of locally administering a therapeutically effective amount of an animal-protein-free botulinum toxin composition, wherein the composition is administered at an interval of time between a first treatment and a second treatment effective to maintain alleviation of at least one symptom of the condition, that is greater than the interval of time for an animal-protein-containing botulinum toxin composition dosed at the same or comparable amount and administered in the same manner (e.g. by injection) to the same locations as that of the animal-protein-free composition.

In certain embodiments, the time between the first treatment and second treatment of a condition in a human patient using an animal-protein-free botulinum toxin composition is at least one month, at least 2 months, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks, at least 16 weeks, at least 17 weeks, at least 18 weeks, at least 19 weeks, at least 20 weeks, at least 21 weeks, at least 22 weeks, at least 23 weeks, at least 24 weeks, at least 25 weeks, at least 26 weeks, at least 27 weeks, at least 28 weeks, at least 29 weeks, at least 30 weeks, at least 31 weeks, at least 32 weeks, at least 33 weeks, at least 34 weeks, at least 35 weeks, at least 36 weeks, at least 37 weeks, at least 38 weeks, at least 39 weeks, at least 40 weeks, at least 41 weeks, at least 42 weeks, at least 43 weeks, at least 44 weeks, at least 45 weeks, at least 46 weeks, at least 47 weeks, at least 48 weeks, at least 49 weeks, at least 50 weeks, at least 51 weeks,

at least 52 weeks or more. In certain embodiments, the time between the first treatment and second treatment using an animal-protein-free botulinum toxin composition is greater than 3 months for the effective alleviation of at least one symptom of a condition in a patient. In certain embodiments, the time between the first treatment and second treatment using an animal-protein-free botulinum toxin composition of the present invention is greater than 16 weeks for the effective alleviation of at least one symptom of a condition in a patient.

In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used for cosmetic purposes such as to treat skin contour deficiencies, including wrinkles, of an individual.

In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used to treat glabellar lines.

In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used to treat lateral canthal lines.

In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used for non-cosmetic purposes. In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used to treat various diseases and disorders including but not limited to detrusor overactivity associated with a neurologic condition, chronic migraine, upper limb spasticity, cervical dystonia, primary axillary hyperhidrosis, blepharospasm and strabismus, idiopathic overactive bladder, and the like.

In certain embodiments, the animal-protein-free botulinum toxin composition of the present invention can be used for non-cosmetic purposes. Non-limiting examples of a non-cosmetic purpose includes but is not limited to the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication, prophylaxis of headaches in patients with chronic migraine (e.g., ≥15 days per month with headache lasting 4 hours a day or longer), treatment of upper limb spasticity in adult patients, treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain, treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents

in adult patients, treatment of blepharospasm associated with dystonia, treatment of strabismus in patients ≥12 years of age.

However, the invention should not be limited to only the diseases, disorder, or conditions disclosed herein. Rather, the invention encompasses the use of the animal-protein-free botulinum toxin composition of the present invention to treat any disease for where botulinum toxin has been used. For example, botulinum toxin has been proposed for or has been used to treat otitis media of the ear (U.S. Pat. No. 5,766,605), inner ear disorders (U.S. Pat. Nos. 6,265,379; 6,358,926), tension headache, (U.S. Pat. No. 6,458,365), migraine headache pain (U.S. Pat. No. 5,714,468), post-operative pain and visceral pain (U.S. Pat. No. 6,464,986), hair growth and hair retention (U.S. Pat. No. 6,299,893), psoriasis and dermatitis (U.S. Pat. No. 5,670,484), injured muscles (U.S. Pat. No. 6,423,319) various cancers (U.S. Pat. Nos. 6,139,845), smooth muscle disorders (U.S. Pat. No. 5,437,291), and neurogenic inflammation (U.S. Pat. No. 6,063,768). In addition, botulinum toxins have been used in clinical settings for cosmetic applications as well as the treatment of neuromuscular disorders characterized by hyperactive skeletal muscles. Botulinum toxin is currently used in the treatment of hyperhidrosis, and can also be used in the treatment of achalasia, chronic focal neuropathies, , anal fissure, vaginismus, spastic disorders associated with injury or disease of the central nervous system (including, for example, trauma, stroke, multiple sclerosis, Parkinson's disease, cerebral palsy, and the like), focal dystonias affecting the limbs, face, jaw, or vocal cords, temporomandibular joint disorder (TMJ), diabetic neuropathy, wound healing disorders, excessive salivation, vocal cord dysfunction (VCD) including spasmodic dysphonia, and tremor. Botulinum toxin type A has been approved by the U.S. Food and Drug Administration for the treatment of blepharospasm, strabismus, hemifacial spasm, cervical dystonia, migraine headaches, overactive bladder and detrusor overactivity associated with a neurological condition.

In certain embodiments, methods of the invention can be useful for the treatment, reduction of symptoms, and/or prevention of achalasia, anal fissure, anismus, blepharospasm, cerebral palsy, cervical dystonia, cervicogenic headache, hemifacial spasm, dyshidrotic eczema, dysphagia, dysphonia, esophageal dysmotility, esophageal muscular ring, esotropia (infantile), eyelift, facial myokemia, gait disturbances

(idiopathic toe-walking), generalized dystonia, hemifacial spasm, hyperfunctional facial lines (glabellar, forehead, crows' feet, down-turned angles of the mouth), hyperhidrosis, incontinence (spinal cord injury), migraine headache, myoclonus, myofascial pain syndrome, obstructive urinary symptoms, pancreas divisum pancreatitis, Parkinson's disease, puborectalis syndrome, reduction of surgical scar tension, salivary hypersecretion, sialocele, sixth nerve palsy, spasticity, speech/voice disorders, strabismus, surgery adjunct (ophthalmic), tardive dyskinesia, temporomandibular joint disorders, tension headache, thoracic outlet syndrome, torsion dystonia, torticolis, Tourette's syndrome, tremor, whiplash-associated neck pain, pain, itching, inflammation, allergy, cancer and benign tumors, fever, obesity, infectious diseases, viral and bacterial, hypertension, cardiac arrhythmias, vasospasm, atherosclerosis, endothelial hyperplasia, venous thrombosis, varicose veins, apthous stomatitis, hypersalivation, temporomandibular joint syndrome, sweating, body odor, acne, rosacea, hyperpigmention, hypertrophic scars, keloid, calluses and corns, skin wrinkling, excessive sebum production, psoriasis, dermatitis, allergic rhinitis, nasal congestion, post nasal drip, sneezing, ear wax, serous and suppurative otitis media, tonsil and adenoid hypertrophy, tinnitus, dizziness, vertigo, hoarseness, cough, sleep apnea, snoring, glaucoma, conjunctivitis, uveitis, strabismus, Grave's disease, asthma, bronchitis, emphysema, mucus production, pleuritis, coagulation disorders, myeloproliferative disorders, disorders involving eosinophils, neutrophils, macrophages and lymphocytes, immune tolerance and transplantation, autoimmune disorders, dysphagia, acid reflux, hiatal hernia, gastritis and hyperacidity, diarrhea and constipation, hemorrhoids, urinary incontinence, prostatic hypertrophy, erectile dysfunction, priapism and Peyronie's disease, epididymitis, contraception, menstrual cramps, preventing premature delivery, endometriosis and fibroids, arthritis, osteoarthritis, rheumatoid, bursitis, tendonitis, tenosynovitis, fibromyalgia, seizure disorders, cerebral palsy, spasticity, headache, depression and neuralgias.

In certain embodiments, the treatment regimen of the invention comprises local administration of the animal-protein-free botulinum toxin composition. In certain embodiments, the treatment regimen comprises parenteral administration of the animal-protein-free botulinum toxin composition. In certain embodiments the animal-protein-

free composition is administered by injection, topically or by implantation of a controlled release implant. Examples of administration by injection include intramuscular injection, non-intramuscular injection, intra-articular injection, extra-articular injection, peri-articular injection, or subcutaneous injection.

In certain embodiments, the treatment regimen of the invention is beneficial due to the longer lasting effect and improved outcomes associated with using animal-protein-free botulinum toxin compositions when compared to using animal-protein-containing botulinum toxin compositions. Without wishing to be bound by any particular theory, it is believed that in certain embodiments the long lasting effect of the animal-protein-free botulinum toxin composition allows for a longer interval time between treatments with the animal-protein-free botulinum toxin composition compared to the interval time when using an animal-protein-containing botulinum toxin composition.

Furthermore, without wishing to be bound by any particular theory, it is believed that in certain embodiments the unique formulation of the compositions using in the invention allows for the longer lasting effect of the composition in the patient.

In certain embodiments, by increasing the interval time between treatments, the treatment regimen allows for a reduction in the frequency of treatment. Therefore, the invention provides the potential for enhanced patient convenience. The increased interval time between treatment and lower frequency of treatment also has the potential to provide reduced side effects.

In certain embodiments, the treatment regimen of the invention is beneficial due to the long lasting effect and improved outcomes associated with using the liquid animal-protein-free botulinum toxin composition or the lyophilized animal-protein-free botulinum composition as described herein.

In certain embodiments, in a treatment method of the invention, a therapeutically effective level botulinum toxin is present in the recipient patient for an extended period of time of at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, at least 26 weeks, at least 28 weeks, at least 30 weeks, at least 32 weeks, at least 34 weeks, at least 36 weeks, at least 38 weeks, at least 40 weeks, at least 42 weeks, at least 44 weeks, at least 46 weeks, at least 48 weeks, at least 50 weeks, or more.

It is to be understood that wherever values and ranges are provided herein, all values and ranges encompassed by these values and ranges, are meant to be encompassed within the scope of the present invention. Moreover, all values that fall within these ranges, as well as the upper or lower limits of a range of values, are also contemplated by the present application.

The following examples further illustrate aspects of the present invention. However, they are in no way a limitation of the teachings or disclosure of the present invention as set forth herein.

EXPERIMENTAL EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

Example 1: The efficacy and safety of liquid type botulinum toxin type A for the management of moderate to severe glabellar frown lines: a parallel, randomized, double-blind, multi-center, active drug controlled, phase III clinical trial

Botulinum toxin A (BoNT/A) has been used widely in a variety of manners to correct unwanted glabellar lines and other hyperfunctional facial lines. However, most of currently using BoNT/A requires dilution with saline solution, which is very inconvenient for the user, and usually is hard to make the exact concentration every time. The results

presented herein is based on experiments conducted that compared the efficacy and safety of newly developed liquid type BoNT/A (MT10109L) and onabotulinumtoxinA (BOTOX®; ona-BoNT/A) for moderate to severe glabellar lines.

The materials and methods employed in these experiments are now described.

Materials and Methods

This study was a prospective, randomized, double-blind, parallel, active drug controlled, Phase III clinical trial for the evaluation of the efficacy and safety of MT10109L on the glabellar frown line correction which was performed in three centers (St. Paul's hospital, Catholic university of Korea; Inha university hospital; Kyunghee university hospital at Gangdong) in South Korea. The study and all appropriate amendments were reviewed and approved by the institutional review board at each participating center in accordance with the guidelines published in the Declaration of Helsinki (South Africa, 1996 amendment) and Good Clinical Practice guideline. All participants gave written informed consent to take part in the study.

Participants

Male and female volunteers aged 20-65 years with glabellar lines were screened by investigators. According to Facial Wrinkle Scale (FWS), subjects with moderate to severe (severity score 2 to 3) glabellar frown lines were enrolled in this study (Table 1). Exclusion criteria included any medical condition (e.g. myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis) that may place the patient at risk with botulinum toxin, prior use of medications that may affect the neuromuscular junction (e.g., muscle relaxants, spectinomycin HCl, aminoglycosides, polypeptide antibiotics, anticholinergics, benzodiazepines) or any allergies or hypersensitivity to the investigational drugs or their components. Other exclusion criteria included previous treatment with botulinum toxin within 3 months, other procedures that may have affected glabellar and forehead lines within 6 months, any history of glabellar treatment (including forehead) such as face lifting and/or permanent implants, or scars that may affect the treatment results. Patients whose glabellar lines that could not be satisfactorily improved even with manual

stretching were also excluded. Patients were not eligible if they had dermatological disorders or infection at potential injection sites, or a history of facial nerve paralysis or ptosis. Pregnant or lactating women were excluded.

Table 1. Scales used to assess the effectiveness of MT10109L and Ona-BoNT/A

Measure	scale	Description
Facial Wrinkle Scale, maximal frown	3	Severe: lines appear clearly formed. The bottoms of the deepest lines are
	2	Moderate: lines appear clearly formed. The bottoms of the deepest lines
	1	Mild: lines noted
	0	None: lines not noted
Facial Wrinkle Scale, rest	3	Severe: lines readily apparent
	2	Moderate: lines noticeable
	1	Mild: lines somewhat noticeable
	0	None: lines not noticeable

Study design

All eligible subjects were randomized into two groups at a 1:1 ratio and followed a 16 weeks duration study design (Fig. 1.). At Visit 2 (0 week, baseline), each subject received a 5 point intramuscular injection with a total dose of 20U (4U/0.1ml) of liquid BoNT/A (MT10109L; Medytox Inc., Cheonwon-gun, Korea) or onabotulinumtoxinA (BOTOX®; ona-BoNT/A) in a double blind manner. The 0.5 mL total injection volume was divided into five injections: 0.1 mL (4 U) in the procerus muscle, 0.1mL (4 U) in each medial corrugator supercilli muscles, and 0.1mL (4 U) in the middle of each corrugator supercilli muscles (Fig. 2). For this clinical study, MT10109L (0.625 ml/vial (4U/0.1ml)) and 50U ona-BoNT/A was used. MT10109L did not require additional dilution for its liquid nature, but ona-BoNT/A was dissolved in 1.25 ml of 0.9% NaCl 1.25ml to make it 4 U per 0.1ml.

Efficacy measures

During the observation period of 16 weeks, the subjects were assessed at 4, 10, 16 weeks. At each visit, both the investigator and the patient assessed efficacy and safety. In addition, standardized digital photographs of the treated facial area were taken in the

same setting using the same equipment (EOS 600d, Canon Inc., Tokyo, Japan) to ensure reproducibility (Fig. 1). Physicians assessed the glabellar line severity at maximum frown and at rest using FWS by live assessment. All investigators in each center were provided the standardized photograph grading system. Three blinded raters assessed the photographs at maximum frown and at rest according to the FWS (Table 1).

The primary efficacy end point was the percentage of responders at maximum frown at week 4 based on the investigator's live assessment (face-to-face observation). Secondary efficacy end point included: 1) percentage of responders at maximum frown at weeks 16; 2) percentage of responders of glabellar lines at rest based on investigator's live assessment at weeks 4 and 16; and 3) percentage of responders at maximum frown and at rest based on photographic assessment at weeks 4. In accordance with previous studies for ona-BoNT/A, responders were defined as those who have post-treatment FWS scores of 0 or 1 with pretreatment FWS scores of 2 or 3. This means an improvement of at least 1 point for the subjects with moderate wrinkles and at least 2 points for the subjects with severe wrinkles. In addition, the glabellar line improvement rates determined by the subject's own assessment and satisfaction rates at weeks 4, 10 and 16 as secondary efficacy end point were also included. Subjects assessed the change of the line severity using 9 point scale from +4 (100% improvement) to 0 (no change) to -4 (100% worse), and rated their degree of satisfaction with the treatment in a 7 point scale from -3 (very unsatisfied) to +3 (very satisfied). Scores of more than +2 points (moderately improved) was considered as improvement. Moreover, scores of more than 6 points (satisfied) were considered as satisfaction.

Safety measures

During the study, physical examination and vital sign were checked every visit. Investigator- and subject-reported signs and symptoms, and laboratory test (Complete Blood Count, and Blood Chemistry) were performed at screening day and weeks 16. Urine-hCG was checked at screening, treatment day, and week 16. Summary and analysis of adverse events was performed about all adverse events occurred after receipt of consent. Incidence of adverse events were documented by comparing incidence of all

adverse events, incidence of adverse events related to study drug, and incidence of severe adverse events.

Statistical methods

All subjects with data for primary end points were included in the full analysis set (FAS). The per protocol (PP) set was the subset of subjects of the FAS who did not commit any major protocol violation. For the primary efficacy end point parameter, the lower limit of 97.5% one-sided confidential interval (CI) for the difference in responder rates between two groups was calculated. The interpretation of the CI was based on the null hypothesis that the expected difference in responder rates between the treatment groups was lower than the non-inferiority margin of -15%. If the lower bound of the estimated CI exceeded the limit of -15%, one could conclude that the MT10109L was not inferior to ona-BoNT/A. This confirmatory analysis was based on the PP analysis. For secondary efficacy end point, paired t- test, Peason's chi-square test, or Fisher's exact test were performed.

Fisher's exact test was performed to test for between-group differences in adverse events. For laboratory variables, blood pressure, and heart rate, the Wilcoxon signed-rank test was performed for within-group analyses, and the Wilcoxon rank-sum test was used for between group analyses of data at exit.

The results of the experiments are now described.

Baseline demographic characteristics

Of 168 subjects enrolled, 159 subjects completed the study and therefore constituted the PP set: 78 subjects in MT10109L group and 81 subjects in ona-BoNT/A group. The enrolled subject's age was from 20 to 65, and the mean age was 48.94 year old in MT10109L group and 49.86 year old in ona-BoNT/A group, respectively. All subjects were Koreans. Demographics of the two groups were comparable, and two groups did not differ in their pretreatment line severity either at rest or maximum frown before treatment. All of subjects had moderate to severe glabellar frown lines at rest and

the majority of subjects had severe glabellar frown lines at maximum frown (56.41% for MT10109L group; 50.62% for ona-BoNT/A group) (Table 2).

Table 2. Subject Demographic Characteristics (N = 159, PP set)

		MT10109L N=78	Ona-BoNT/A N=81	*p*-value
		n (%)	n (%)	
Age	n	78	81	
	Mean±SD	48.94±9.13	49.86±9.13	0.5226*
	20~29	3(3.85)	3(3.70)	0.8081†
	30~39	7(8.97)	9(11.11)	
	40~49	28(35.90)	22(27.16)	
	50~59	32(41.03)	39(48.15)	
	60~65	8(10.26)	8(9.88)	
Gender	n	78	81	
	male	19(24.36)	15(18.52)	0.3692†
	female	59(75.64)	66(81.48)	
Botulinumtoxin injections history	n	78	81	
	yes	15(19.23)	12(14.81)	0.4585†
	no	63(80.77)	69(85.19)	
No. of Botulinumtoxin injections	n	15	12	
	Mean±SD	1.93±0.26	2.00±0.43	0.6547+
Elapsed time after the administration of botulinumtoxin injections (month)	n	15	12	
	Mean±SD	22.18±13.28	20.31±16.44	0.6428+
at screening,	n	78	81	
investigator's live assessment	3 (severe)	44(56.41)	41(50.62)	0.4641†
at maximum frown (point)	2 (moderate)	34(43.59)	40(49.38)	

*: two sample t-test

+: Wilcoxon rank sum test

†: Pearson's chi-square test

Investigator's assessment

Both groups showed significant improvement of glabellar lines. Four weeks after injection, percentage of responders at maximum frown by live assessment for the PP set was 87.18% in MT10109L group and 87.65% in ona-BoNT/A group. In addition, percentage of responders of FAS in MT10109L group and ona-BoNT/A group was similar to that of PP set, being 85.54% and 85.71%, respectively (Figure 3A). The 97.5 % CIs for the difference in percentage of responders between the two treatment groups (-

10.79 % for PP > -15%; -10.47 % for FAS > -15%) demonstrates that MT10109L was not inferior to ona-BoNT/A.

The percentage of responders at maximum frown by live assessment at weeks 16 was significantly lower in ona-BoNT/A group than MT10109L group. The percentage of responders in PP set was 62.34% in MT10109L group and 40.51% in ona-BoNT/A group (p value = 0.0064) (Table 3). And the percentage of responders in FAS set was 60.71% in MT10109L group and 41.67% in ona-BoNT/A group (Table 3, Figure 3B). Both PP set and FAS set showed significant difference in two groups and superiority of MT10109L.

The percentage of responders at rest was assessed at week 4 and 16, and no significant difference was noted between the MT10109L group and ona-BoNT/A group at week 4 in both PP set and FAS set. At week 16, percentage of responders at rest in PP set was 50.00 % in MT10109L group and 31.58 % in ona-BoNT/A group, showing significant improvement in MT10109L group (p value = 0.0482). However, in the FAS set, the percentage of responders did not show significant difference between the MT10109L group (50.00%) and the ona-BoNT/A group (33.33%). (p value: 0.0641) (Table 3).

Table 3. Responder rate by live assessment at maximum frown

			MT10109L n (%)	Ona-BoNT/A n (%)	*p*-value
PP set			**N=78**	**N=81**	
Week 4	Improvement	n	78	81	
		Responder	68 (87.18)	71 (87.65)	0.9281†
		non-responder	10 (12.82)	10 (12.35)	
	Facial Wrinkle Scale	3	1 (1.28)	0 (0)	
		2	9 (11.54)	10 (12.35)	
		1	39 (50)	44 (54.32)	
		0	29 (37.18)	27 (33.33)	
Week 16	Improvement	n	77	79	
		Responder	48 (62.34)	32 (40.51)	0.0064†
		non-responder	29 (37.66)	47 (59.49)	
	Facial Wrinkle Scale	3	8 (10.39)	8 (10.13)	
		2	21 (27.27)	39 (49.37)	
		1	36 (46.75)	25 (31.65)	
		0	12 (15.58)	7 (8.86)	
FAS set			**N=84**	**N=84**	
Week 4	Improvement	n	83	84	
		Responder	71 (85.54)	72 (85.71)	0.9747†
		non-responder	12 (14.46)	12 (14.29)	
	Facial Wrinkle Scale	3	1 (1.2)	1 (1.19)	
		2	11 (13.25)	11 (13.1)	
		1	41 (49.4)	45 (53.57)	
		0	30 (36.14)	27 (32.14)	
Week 16	Improvement	n	84	84	
		Responder	51 (60.71)	35 (41.67)	0.0135†
		non-responder	33 (39.29)	49 (58.33)	
	Facial Wrinkle Scale	3	8 (9.52)	9 (10.71)	
		2	25 (29.76)	40 (47.62)	
		1	39 (46.43)	26 (30.95)	
		0	12 (14.29)	9 (10.71)	

†: Pearson's chi-square test

In photographic assessment, the responder rate at maximum frown at weeks 4 by three independent, blinded raters also did not show significant difference between the

MT10109L group and the ona-BoNT/A group in PP set and FAS set. The results are shown in Table 4.

Table 4. Responder rate by photo assessment (Weeks 4)

			MT10109L n (%)	Ona-BoNT/A n (%)	*p*-value
Maximum frown	PP set	n	78	81	
		Responder	74 (94.87)	79 (97.53)	0.4369‡
		non-responder	4 (5.13)	2 (2.47)	
	FAS set	n	83	84	
		Responder	79 (95.18)	82 -97.62	0.4431‡
		non-responder	4 (4.82)	2 -2.38	
Resting	PP set	n	44	47	
		Responder	25 (56.82)	25 (53.19)	0.7282†
		non-responder	19 (43.18)	22 (46.81)	
	FAS set	n	48	49	
		Responder	26 (54.17)	25 (51.02)	0.7564†
		non-responder	22 (45.83)	24 (48.98)	

Subject's assessment

Subject's assessment on improvement of glabellar line and satisfaction yielded comparable results for both groups. Peak improvement rate defined as the proportion of subjects who scored more than +2 points (moderately improved) were assessed at week 4, 10, and 16. In both PP set and FAS set, the peak improvement rate at week 4, 10, and 16 did not show significant difference between MT10109L and ona-BoNT/A groups. Subjective-assessment improvement rate was shown 89.74% and 92.59% at week4, 81.82% and 91.14% at week10, 70.13% and 68.35% at week16, respectively in MT10109L and ona-BoNT/A group of PP set. Satisfaction rate defined as patient showing "very satisfied" or "satisfied" was assessed at week 4, 10, 16, and this also did not show significant difference in PP set and FAS set between MT10109L and ona-BoNT/A groups. Satisfaction rate was 78.21% and 71.60% at week4, 74.03% and

68.35% at week10, 58.44% and 48.10% at week16, respectively in MT10109L and ona-BoNT/A group of PP set. The results of PP set are shown in Figure 4.

Safety

Comparable numbers of treatment-emergent adverse events were reported in the MT10109L group (21.43%) and the control group (16.67%) (Table 5). There was no adverse drug reaction in MT10109L group. The only adverse drug reaction related to injection was one incident of face edema reported in the control group. No severe adverse drug reaction was observed in both groups. No subjects were withdrawn because of adverse events.

Table 5. Adverse events (safety set)

adverse events (n. %)	MT10109L group (N=84)	Ona-BoNT/A (N=84)	*p*-value
adverse events	19 (22.62)	15 (17.86)	0.4424
treatment-emergent adverse events	18 (21.43)	14 (16.67)	0.4319
adverse drug reaction			
facial edema	0 (0.00)	1 (1.19)	1
severe adverse events			
acute myocardial infarction	0 (0.00)	1 (1.19)	1
peritonitis	0 (0.00)	1 (1.19)	1
rotator cuff syndrome	1 (1.19)	0 (0.00)	1

Serious adverse events happening after the patient receiving the test medication were reported in 1.19% (1/84 subjects, 1 incidents) of the MT10109L group and 2.38% (2/84 subjects, 2 incidents) of the control group. For serious adverse events, acute myocardial infarction and peritonitis was reported in each patient of ona-BoNT/A group. The patient who developed acute myocardial infarction have been treated for his cardiac problem in the cardiology department, thus, this event does not seem to be related to test drug injection. And Rotator cuff syndrome was reported in one patient of MT10109L group after the patient received the test medication.

In terms of the laboratory tests and vital signs, no significant abnormal changes were detected after the test drug administration in MT10109L group and ona-BoNT/A group.

The efficacy and safety of liquid type botulinum toxin type A

The results presented herein demonstrate that MT10109L is safe and effective for the treatment of glabellar lines. MT10109L treatment resulted in significant improvement of glabella frown line severity at both maximal contraction and rest by live assessment at week 4 and week 16. The results of photographic assessment by blinded raters and subject's assessment in this study indicate that ona-BoNT/A and MT10109L did not differ significantly in any variable at any point. The result also showed that MT10109L may provide greater improvement than ona-BoNT/A at week 16. The results presented here also suggest that efficacy of MT10109L persisted longer than ona-BoNT/A.

Commercially available BoNT/A preparations were very diverse and had different efficacies and safety because of their unique biologic nature (Klein AW, et al., Plast Reconstr Surg., 2008; 121(6):413e-422e). Of these, ona-BoNT/A is the best known type which dominates the botulinum toxin market since it was first approved and marketed in the United States in 1989 (Yang GH, et al., Dermatologic Surgery, 2013; 39(1pt2):165-170). As a consequence, the majority of the information about handling botulinum toxin type A is found with ona-BoNT/A (Trindade De Almeida AR, et al., Dermatologic Surgery, 2011; 37(11):1553-1565), Thus, this study was designed to compare the efficacy and safety of MT10109L and ona-BoNT/A.

All of the currently used BoNT/A products recommend that reconstitution be performed using variable substances before injection since the products are provided as freeze dried powder formulation. These products also have discommodity on supply, dilution and storage. For example, Ona-BoNT/A should be stored between 2°C and 8°C after reconstitution, and is to be used within 24 hours of reconstitution (Huang W, et al., J Am Acad Dermatol 2000; 43:249–59).

Although rimabotulinumtoxin b (Myobloc®, Solstice Neurosciences, Louisville, KY) has been used as liquid injection form of botulinum toxin B, it is not widely used as much as BoNT/A and the equivalent dosage of rimabotulinumtoxin b with BoNT/A has not been fully studied (Trindade De Almeida AR, et al., Dermatologic Surgery, 2011; 37(11):1553-1565).

MT10109L is the first liquid injection form of BoNT/A. MT10109L contains BoNT/A type macromolecular protein complexes with molecular weights of 900 kD,

which is similar to ona-BoNT/A (Table 6). MT10109L exhibits a similar diffusion capacity to that of ona-BoNT/A.

MT10109L is provided as a ready-to-use sterile liquid; no reconstitution is required and is more convenient to store and reuse compared to most of BoNT/A. The shelf life of MT10109L is currently estimated at around 22 months from the date of manufacture, however, without wishing to be bound by any particular theory, it is expected to be prolonged through extended stability test. During the period, MT10109L can be reused at anytime without time limit, whereas ona-BoNT/A is recommended to be used within 4 hours to 6 weeks after reconstitution (Carruthers J, et al., Plast Reconstr Surg., 2004; (Suppl); 11(6)4:2S and Hexsel DM, et al., Dermatol Surg., 2003; 29:523–9). Because longer stability of MT10109L is validated as mentioned elsewhere herein, MT10109L has an advantage over reconstituted ona-BoNT/A in reusing. Moreover, MT10109L is currently available as small package unit (25 U/vial), which is suitable for treatment of glabellar lines (Table 6).

Table 6. Charateristics of botulinum Toxin Preparations

	MT10109L	Ona-BoNT/A
Manufaturer	Medytox Inc.	Allergan, Inc.
Commercial names	Neuranox Aqua®	Botox®, Botox cosmetic®, Vistabel®, Vistabex®
Toxin serotype	A	A
Indications	glabellar lines	Blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, chronic migraine
Active substance	Botulinum Toxin Type A	Botulinum Toxin Type A
Complex molecular weight	900 kDa	900 kDa
U/vial	25	50
Stabilizer/vial	methionine (0.125 mg) polysorbate 20 (0.094 mg)	Human serum albumin (0.5 mg)
Excipients/vial	sodium chloride (5.625 mg)	sodium chloride (0.45 mg)
Formulation	liquid	vacuum-dried powder
Dilution, mL	No reconstitution required	1.0–2.5
Storage	2–8°C	2–8°C or < -5°C
Storage after dilution/temperature	without limitation/2–8°C	24 hours/2–8°C

The results presented herein demonstrate that the efficacy of MT10109L persisted longer than ona-BoNT/A. The therapeutic effect of BoNT/A for the glabellar line improvement could be detected within 4 weeks after injection and gradually decrease between 3-6 months. The fact that a longer maintaining period of the glabellar line improvement associated with the use of MT10109L provides a great advantage over other types of BoNT/A. Results from a meta-analysis by Glogau R, et al. showed treatment of glabellar line with 20 unit of ona-BoNT/A sustained clinical effect at week 16 in more than 50% of responders (Glogau R, et al., Dermatol Surg., 2012; 38(11):1794-803). However, in this study, responder rate of ona-BoNT/A was lower than that of previous reports. Thus, large studies, with enrollment of patients from several medical centers and with longer follow-up periods, are needed to confirm this result.

Whereas currently used BoNT/A contain albumin or gelatin for stabilization, MT10109L eliminated albumin but also animal derived materials in component of the entire manufacturing process. Therefore, MT10109L minimized risk of infectious diseases which included transmissible spongiform encephalopathy. No severe adverse drug reactions with either toxin were observed in the present study. Therefore, MT10109L is as safe as ona-BoNT/A.

The results presented herein demonstrate that MT10109L is not inferior to ona-BoNT/A in the improvement of glabellar lines and is relatively similar in safety, which therefore can be judged to be used in the treatment of the relevant symptom. With its longer maintaining period of the glabellar line improvement, convenience without the additional dilution step, easy storage and re-usage, and animal derived protein-free constituents, MT10109L is a desirable substitute for the conventional powder formulation of BoNT/A.

Example 2: Randomized, Double-blind, Multi-center, Phase II, Optimal Dose-finding Study to Determine Safety and Efficacy of MT10109 v. BOTOX in Subjects with Moderate to Severe Glabellar Lines

The results presented herein compare the safety and efficacy of lyophilized formulation of MT10109 and BOTOX® in subjects with moderate to severe glabellar

lines. It is demonstrated that the response at maximum frown was sustained in the MT10109 20U group for up to 120 days.

The experiments described herein compared dosing of MT10109 at 10U, 20U and 30U to BOTOX® dosed at 20U. The efficacy of MT10109 was primarily assessed at Day 30 (Visit 4; ± 7 days) and the comparison of interest was the comparison between the responder rates for MT10109 20 U and BOTOX® 20 U. A responder was defined as a glabellar line severity rating of none (0) or mild (1) at maximum frown or at rest at Day 30, depending on the analysis.

The time points of Day 14 (Visit 3), Day 30 (Visit 4), Day 60 (Visit 5), Day 90 (Visit 6) and Day 120 (Visit 7) were allowed 7 days either side of the visit day and so Day 30, for example, may not be exactly 30 days after study treatment administration. As presented herein, time points have been labelled by day rather than visit. All analyses of efficacy were performed using the Full Analysis Set (FAS) and were repeated using the Per-protocol (PP) Set as a supportive analysis.

Primary Efficacy Parameter: Investigator's Rating of Glabellar Line Severity at Maximum Frown at Day 30 by Live Assessment

The investigator's live assessment of glabellar line severity at maximum frown at Day 30 is summarized for the FAS in Table 7. A Mantel-Haenszel chi-square test was used to compare treatment groups and is in diagram form in Figure 5. Results for the PP Set are summarized in Table 8.

Table 7: Investigator's Live Assessment of Glabellar Line Severity at Maximum Frown at Day 30, Full Analysis Set

Live Assessment of Glabellar Lines	**MT10109 10U N=31 n (%)**	**MT10109 20U N=28 n (%)**	**MT10109 30U N=26 n (%)**	**BOTOX 20U N=29 n (%)**
Day 30, at maximum frown	**n=30**	**n=26**	**n=25**	**n=26**
Responders	18 (60.0)	18 (69.2)	22 (88.0)	19 (73.1)
Non-responders	12 (40.0)	8 (30.8)	3 (12.0)	7 (26.9)

Abbreviations: N=number of subjects in analysis set; n=number of subjects with data.
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating at maximum frown of moderate (2) or severe (3). A responder was defined as having a severity rating of none (0) or mild (1) at the corresponding post-baseline visit. Percentages are based on the number of subjects with an assessment at the relevant visit.

For the FAS, based on the investigator's live assessment of subjects' glabellar line severity at maximum frown at Day 30, the proportion of responders (a severity rating of none [0] or mild [1]) in the MT10109 20 U group was similar to that in the BOTOX® 20 U group (Table 7).

The proportion of responders in the MT10109 20 U group was 69.2% (18 of 26 subjects) and in the BOTOX® 20 U group was 73.1% (19 of 26 subjects).

There was no statistically significant difference between the proportion of responders in the MT10109 20 U and BOTOX® 20 U groups (-3.2 [95% CI: -28.3 to 21.8]; p-value 0.760) (Figure 5).

The proportion of responders in the MT10109 10 U group was smaller compared with the BOTOX® 20 U group and the proportion of responders in the MT10109 30 U group was greater compared with BOTOX® 20 U (Table 7).

The proportion of responders in the MT10109 10 U group was 60.0% (18 of 30 subjects) and in the MT10109 30 U group was 88.0% (22 of 25 subjects) and in the BOTOX® 20 U group was 73.1% (19 of 26 subjects).

There was no statistically significant difference between the proportion of responders in the MT10109 10 U and BOTOX® 20 U groups (-9.7 [95% CI: -34.6 to 15.2]; p-value 0.448), or between the MT10109 30 U and BOTOX® 20 U groups (17.6 [95% CI: -4.1 to 39.3]; p-value 0.117) (Figure 5).

There was no statistically significant difference between the proportion of responders in the MT10109 10 U and MT10109 20 U groups (-6.5 [95% CI: -31.4 to 18.4]; p-value 0.614), or between the proportion of responders in the MT10109 30 U and MT10109 20 U groups (20.8 [95% CI: -0.9 to 42.5]; p-value 0.066). The proportion of responders in the MT10109 10 U group was smaller than that of the MT10109 30 U group and the difference was statistically significant (-27.3 [95% CI: -48.8 to -5.8]; p-value 0.020).

The investigator's live assessment of glabellar line severity at maximum frown at Day 30 is summarized for the PP Set in Table 8. A Mantel-Haenszel chi-square test was used to compare treatment groups.

Table 8: Investigator's Live Assessment Rating of Glabellar Line Severity at Maximum Frown at Day 30, Per-protocol Set

Live Assessment of Glabellar Lines	MT10109 10U N=30 n (%)	MT10109 20U N=26 n (%)	MT10109 30U N=23 n (%)	BOTOX 20U N=26 n (%)
Day 30, at maximum frown	**n=30**	**n=26**	**n=23**	**n=26**
Responders	18 (60.0)	18 (69.2)	20 (87.0)	19 (73.1)
Non-responders	12 (40.0)	8 (30.8)	3 (13.0)	7 (26.9)

Abbreviations: N=number of subjects in analysis set; n=number of subjects with data.
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a severity rating of none (0) or mild (1) at the corresponding post-baseline visit. Percentages are based on the number of subjects with an assessment at the relevant visit.

The results in the PP Set supported those in the FAS.

The proportion of responders in the MT10109 20 U group was 69.2% (18 of 26 subjects) and in the BOTOX® 20 U group was 73.1% (19 of 26 subjects) (Table 8).

The difference between the proportion of responders in the MT10109 20 U and BOTOX® 20 U groups was -3.8 (95% CI: -32.8 to 25.1; p-value 0.762) which was not statistically significant.

The proportion of responders in the PP Set in the MT10109 10 U group was smaller compared with the BOTOX® 20 U group and the proportion of responders in the MT10109 30 U group was greater compared with BOTOX® 20 U:

The proportion of responders in the MT10109 10 U group was 60.0% (18 of 30 subjects) and in the MT10109 30 U group was 87.0% (20 of 23 subjects) and in the BOTOX® 20 U group was 73.1% (19 of 26 subjects) (Table 8).

There was no statistically significant difference between the proportion of responders in the MT10109 10 U and BOTOX® 20 U groups (-13.1 [95% CI: -41.6 to 15.4]; p-value 0.307), or between the MT10109 30 U and BOTOX® 20 U groups (13.9 [95% CI: -12.6 to 40.3]; p-value 0.234).

Secondary Efficacy Parameter: Investigator's Rating of Glabellar Line Severity at Maximum Frown and at Rest up to Day 120 by Live Assessment

The investigator's live assessment of glabellar line severity at maximum frown and rest at other visits is summarized for the FAS in Table 9, and in diagram form in Figure 6. A Mantel-Haenszel chi square test was used to compare treatment groups.

Table 9: Investigator's Live Assessment Rating of Glabellar Line Severity at Other Visits, Full Analysis Set

Live Assessment of Glabellar Lines	MT10109 10U N=31 n (%)	MT10109 20U N=28 n (%)	MT10109 30U N=26 n (%)	BOTOX 20U N=29 n (%)
Day 14, at maximum frown	**n=31**	**n=28**	**n=25**	**n=28**
Responders	18 (58.1)	20 (71.4)	22 (88.0)	22 (78.6)
Non-responders	13 (41.9)	8 (28.6)	3 (12.0)	6 (21.4)
Day 14, at rest	**n=13**	**n=12**	**n=14**	**n=11**
Responders	4 (30.8)	3 (25.0)	8 (57.1)	7 (63.6)
Non-responders	9 (69.2)	9 (75.0)	6 (42.9)	4 (36.4)
Day 30, at rest	**n=12**	**n=10**	**n=13**	**n=9**
Responders	4 (33.3)	1 (10.0)	6 (46.2)	5 (55.6)
Non-responders	8 (66.7)	9 (90.0)	7 (53.8)	4 (44.4)
Day 60, at maximum frown	**n=30**	**n=23**	**n=25**	**n=25**
Responders	15 (50.0)	15 (65.2)	17 (68.0)	17 (68.0)
Non-responders	15 (50.0)	8 (34.8)	8 (32.0)	8 (32.0)
Day 60, at rest	**n=12**	**n=10**	**n=13**	**n=10**
Responders	4 (33.3)	1 (10.0)	7 (53.8)	4 (40.0)
Non-responders	8 (66.7)	9 (90.0)	6 (46.2)	6 (60.0)
Day 120, at maximum frown	**n=28**	**n=23**	**n=25**	**n=26**
Responders	9 (32.1)	12 (52.2)	7 (28.0)	6 (23.1)
Non-responders	19 (67.9)	11 (47.8)	18 (72.0)	20 (76.9)
Day 120, at rest	**n=10**	**n=10**	**n=13**	**n=10**
Responders	1 (10.0)	1 (10.0)	5 (38.5)	3 (30.0)
Non-responders	9 (90.0)	9 (90.0)	8 (61.5)	7 (70.0)

Abbreviations: N=number of subjects in analysis set; n=number of eligible subjects with data.
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a severity rating of none (0) or mild (1) at the corresponding post-baseline visit. Percentages are based on the number of eligible subjects with an assessment at the relevant visit.

The proportion of responders at maximum frown decreased in all treatment groups from Day 14 to Day 120 (based on the investigator's live assessment). The proportions at Day 120 were greater in the MT10109 20 U group compared with BOTOX® 20 U and the other MT10109 groups (Figure 6).

The proportion of responders at maximum frown in the MT10109 20 U group at Day 60, and at Day 120 was 65.2% (15 of 23 subjects) and 52.2% (12 of 23 subjects), respectively, and in the BOTOX® 20 U group was 68.0% (17 of 25 subjects) and 23.1% (6 of 26 subjects), respectively (Table 9).

The difference between the proportion of responders in the MT10109 20 U and BOTOX® 20 U groups at maximum frown at Day 60 was -4.3 (95% CI: -30.7 to 22.1; p-value 0.714) and at Day 120 was 24.0 (-0.7 to 48.7; p-value 0.058).

In the other MT10109 groups, the proportions of responders at maximum frown at Day 60 were smaller in the MT10109 10 U group (50.0%; 15 of 30 subjects) and similar in the MT10109 30 U group (68.0%; 17 of 25 subjects) compared with the BOTOX® 20 U group (68.0%; 17 of 25 subjects). At Day 120 proportions were greater in the MT10109 10 U (32.1%; 9 of 28 subjects) and MT10109 30 U (28.0%; 7 of 25 subjects) groups than in the BOTOX® 20 U group (23.1%;6 of 26 subjects) (Table 9). There was no statistically significant difference in the proportion of responders at maximum frown between the MT10109 10 U and BOTOX® 20 U groups or between the MT10109 30 U and BOTOX® 20 U groups at any time point. There was no statistically significant difference in the proportion of responders at maximum frown between the MT10109 10 U and MT10109 20 U groups, or between the MT10109 30 U and MT10109 20 U groups at any time point. The proportion of responders in the MT10109 10 U group was generally smaller than in the MT10109 30 U group and the difference was statistically significant at Day 14 (-30.4 [95% CI: -55.6 to -5.2]; p-value 0.012).

In the analyses of the investigator's live assessment of glabellar line severity at rest, the number of subjects who were eligible for inclusion in the analysis (i.e., baseline glabellar line severity of either moderate [2] or severe [3]) was small. Consequently, comparisons between treatment groups and any resulting p-values should be treated with caution.

The proportion of responders at rest decreased in all treatment groups from Day 14 to Day 120 (based on the investigator's live assessment) (Figure 9 center left). The proportions were smaller in the MT10109 20 U group compared with the BOTOX® 20 U group at every time point.

The proportion of responders at rest in the MT10109 20 U group at Day 14 and at Day 120 was 25.0% (3 of 12 subjects) and 10.0% (1 of 10 subjects), respectively, and in the BOTOX® 20 U group was 63.6% (7 of 11 subjects) and 30.0% (3 of 10 subjects), respectively (Table 9).

Proportions of responders at rest at Day 120 were smaller in the MT10109 10 U (10.0%; 1 of 10 subjects) and greater in the MT10109 30 U (38.5%; 5 of 13 subjects) groups than in the BOTOX® 20 U group (30.0%; 3 of 10 subjects) (Table 9).

Secondary Efficacy Parameter: Subject's Assessment of Glabellar Line Improvement and Satisfaction with Effect of Treatment

The subject's self-assessment of glabellar line improvement is summarized in Table 10 and in diagram form in Figure 7. The subject's self-assessment of satisfaction with the effect of treatment is summarized in Table 11 and in diagram form in Figure 8. A Mantel-Haenszel chi square test was used to compare treatment.

Table 10: Subject's Self-assessment of Glabellar Line Improvement, Full Analysis Set

Self-assessment Improvement	MT10109 10U N=31 n (%)	MT10109 20U N=28 n (%)	MT10109 30U N=26 n (%)	BOTOX 20U N=29 n (%)
Day 14	**n=31**	**n=28**	**n=25**	**n=28**
Responders	18 (58.1)	21 (75.0)	22 (88.0)	23 (82.1)
Non-responders	13 (41.9)	7 (25.0)	3 (12.0)	5 (17.9)
Day 30	**n=30**	**n=26**	**n=25**	**n=26**
Responders	16 (53.3)	19 (73.1)	19 (76.0)	18 (69.2)
Non-responders	14 (46.7)	7 (26.9)	6 (24.0)	8 (30.8)
Day 60	**n=30**	**n=23**	**n=25**	**n=25**
Responders	13 (43.3)	15 (65.2)	17 (68.0)	13 (52.0)
Non-responders	17 (56.7)	8 (34.8)	8 (32.0)	12 (48.0)
Day 90	**n=30**	**n=25**	**n=25**	**n=26**
Responders	6 (20.0)	14 (56.0)	10 (40.0)	9 (34.6)
Non-responders	24 (80.0)	11 (44.0)	15 (60.0)	17 (65.4)
Day 120	**n=28**	**n=23**	**n=25**	**n=26**
Responders	8 (28.6)	10 (43.5)	7 (28.0)	8 (30.8)
Non-responders	20 (71.4)	13 (56.5)	18 (72.0)	18 (69.2)

Abbreviations: N=number of subjects in analysis set; n=number of subjects with data.
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least +2 (moderate improvement, about 50%) on the 9-point scale. Percentages are based on the number of subjects with an assessment at the relevant visit.

In the subject's self-assessment of glabellar line improvement, the proportions of responders (a score of at least +2 [moderate improvement, about 50%] on the 9-point scale) at Day 30 were similar across the MT10109 20 U and BOTOX® 20 U groups (FAS), which reflected the live assessment ratings. The proportions were also similar across the MT10109 30 U and BOTOX® 20 U groups. At Day 60 the proportions were greater in the MT10109 20 U and MT10109 30 U groups than the BOTOX® 20 U group and at Day 120, the proportions remained greater in the MT10109 20 U group compared with the other treatment groups (Figure 7).

The proportion of responders in the MT10109 20 U group at Day 30, Day 60 and Day 120 was 73.1% (19 of 26 subjects), 65.2% (15 of 23 subjects) and 43.5% (10 of 23 subjects), respectively, and in the BOTOX® 20 U group was 69.2% (18 of 26 subjects), 52.0% (13 of 25 subjects) and 30.8% (8 of 26 subjects), respectively (Table 10). There was no statistically significant difference between the proportion of responders in the MT10109 20 U and BOTOX® 20 U groups at any time point.

In the other MT10109 groups, at Day 30 and Day 60, proportions of responders were smaller in the MT10109 10 U group and greater in the MT10109 30 U group compared with the BOTOX® 20 U group (Table 10). At Day 120, proportions were similar across the three treatment groups (MT10109 10 U, 28.6% [8 of 28 subjects]; MT10109 30 U, 28.0% [7 of 25 subjects]; BOTOX® 20 U, 30.8% [8 of 26 subjects]). The difference in the proportion of responders between MT10109 10 U and BOTOX® 20 U at Day 14 was statistically significant (-23.6 [95% CI: -46.5 to -0.6]; p-value 0.049). No statistically significant difference between the proportion of responders in the MT10109 30 U and BOTOX® 20 U groups was observed at any time point. There was no statistically significant difference in the proportion of responders in the subject's assessment of glabellar line improvement between the MT10109 30 U and MT10109 20 U groups. The proportion of responders in the MT10109 10 U group was smaller than in the other two groups at each time point. The difference was statistically significant between the MT10109 10 U and MT10109 30 U groups at Day 14 (-30.4 [95% CI: -52.0 to -8.7]; p-value 0.011) and between the MT10109 10 U and MT10109 20 U groups at Day 90 (-34.7 [95% CI: -58.8 to -10.7]; p-value 0.007).

Table11: Subject's Self-assessment of Satisfaction with the Effect of the Treatment, Full Analysis Set

Self-assessment Satisfaction	MT10109 10U N=31 n (%)	MT10109 20U N=28 n (%)	MT10109 30U N=26 n (%)	BOTOX 20U N=29 n (%)
Day 14	**n=31**	**n=28**	**n=25**	**n=28**
Responders	16 (51.6)	20 (71.4)	19 (76.0)	17 (60.7)
Non-responders	15 (48.4)	8 (28.6)	6 (24.0)	11 (39.3)
Day 30	**n=30**	**n=26**	**n=25**	**n=26**
Responders	13 (43.3)	17 (65.4)	18 (72.0)	16 (61.5)
Non-responders	17 (56.7)	9 (34.6)	7 (28.0)	10 (38.5)
Day 60	**n=30**	**n=23**	**n=25**	**n=25**
Responders	14 (46.7)	14 (60.9)	13 (52.0)	11 (44.0)
Non-responders	16 (53.3)	9 (39.1)	12 (48.0)	14 (56.0)
Day 90	**n=30**	**n=25**	**n=25**	**n=26**
Responders	10 (33.3)	14 (56.0)	15 (60.0)	9 (34.6)
Non-responders	20 (66.7)	11 (44.0)	10 (40.0)	17 (65.4)
Day 120	**n=28**	**n=23**	**n=25**	**n=26**
Responders	11 (39.3)	13 (56.5)	11 (44.0)	12 (46.2)
Non-responders	17 (60.7)	10 (43.5)	14 (56.0)	14 (53.8)

Abbreviations: N=number of subjects in analysis set; n=number of subjects with data.
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least 6 (satisfied) on the 7-point scale. Percentages are based on the number of subjects with an assessment at the relevant visit.

In the subject's self-assessment of satisfaction with the effect of treatment, a responder was defined as having a score of at least 6 (satisfied) on the 7-point scale.

As seen in the self-assessment of improvement, the proportion of responders in the assessment of satisfaction at Day 30 were similar in both the MT10109 20 U and BOTOX® 20 U groups, which reflected the live assessment ratings. At Day 120, the responder rate was greater in the MT10109 20 U group than any other treatment group (Figure 8). Satisfaction appeared consistent in the MT10109 20 U group but a pattern was hard to discern in the BOTOX® 20 U and other MT10109 groups.

The proportion of responders in the MT10109 20 U group at Day 30, Day 60 and Day 120 was 65.4% (17 of 26 subjects), 60.9% (14 of 23 subjects) and 56.5% (13 of 23 subjects), respectively, and in the BOTOX® 20 U group was 61.5% (16 of 26 subjects), 44.0% (11 of 25 subjects) and 46.2% (12 of 26 subjects), respectively (Table 11). There was no statistically significant difference in the proportion of responders between the MT10109 20 U and BOTOX® 20 U groups at any time point.

In the other MT10109 groups, at Day 30, proportions of responders were smaller in the MT10109 10 U group and greater in the MT10109 30 U group compared with the BOTOX® 20 U group (Table 11). At Day 60, proportions were greater in both MT10109 groups compared with BOTOX® 20 U. At Day 120, proportions were smaller in the MT10109 10 U (39.3% [11 of 28 subjects]) and MT10109 30 U (44.0% [11 of 25 subjects]) treatment groups compared with the BOTOX® 20 U group (46.2% [12 of 26 subjects]). No statistically significant difference in the proportion of responders between the MT10109 10 U and BOTOX® 20 U groups or the MT10109 30 U and BOTOX® 20 U groups was observed at any time point.

There was no statistically significant difference in the proportion of responders in the subject's assessment of satisfaction with the effect of treatment between the MT10109 10 U and MT10109 20 U groups, or between the MT10109 30 U and MT10109 20 U groups. The proportion of responders in the MT10109 10 U group was smaller than in the MT10109 30 U group at each time point and the difference was statistically significant at Day 30 (-27.3 [95% CI: -52.8 to -1.9]; p-value 0.040).

Efficacy Results (FAS) – Improved sustained efficacy of MT10109

MT10109 at a single dose of 20 U demonstrated a similar effect to that of BOTOX® 20 U in reducing subjects' glabellar lines.

After the investigator's live assessment of glabellar line severity at maximum frown at Day 30, the proportion of responders in the MT10109 20 U group was 69.2% and in the BOTOX® 20 U group was 73.1%. The difference between the proportion of responders in the two treatment groups was -3.2 (95% CI: -28.3 to 21.8) which was not statistically significant (p-value 0.760).

In the subject's self-assessment of glabellar line improvement and satisfaction with the effect of treatment, proportions of responders were generally greater in the MT10109 20 U and MT10109 30 U groups compared with BOTOX® 20 U. At Day 30, responder rates in the MT10109 20 U and BOTOX® 20 U groups were similar, reflecting the live assessment ratings (MT10109 20 U group, 73.1% for improvement and 65.4% for satisfaction with treatment effect; BOTOX® 20 U group, 69.2% and 61.5%, respectively).

The response at maximum frown was sustained in the MT10109 20 U group to Day 120. The proportion of responders at Day 120, according to the investigator's live assessment, was 52.2% in the MT10109 20 U group compared with 23.1% in the BOTOX® 20 U group. At most time points, proportions of responders at maximum frown were greater in the MT10109 30 U group and smaller in the MT10109 10 U group compared with the BOTOX® 20 U group.

Fewer subjects were considered responders by the independent reviewers based on the photographic assessment; however, the proportions of responders (using the mean score) at maximum frown at Day 30 and Day 60 were similar in the MT10109 20 U (48.1% and 40.7%, respectively) and BOTOX® 20 U treatment groups (51.7% and 41.4%, respectively), which reflected the investigator's live assessment.

In both the investigator's live assessment and independent reviewers' photographic assessment of glabellar lines severity at rest, the proportions of responders were small across all treatment groups. At most time points, the responder rates were smaller in the MT10109 20 U group compared with the BOTOX® 20 U group.

Using a logistic regression at Day 30 and at maximum frown, the dose-response curve showed no relationship between dose and response.

The data from the experiments is further illustrated in Figure 9 and Figure 10. Figure 9 presents a series of graphs depicting investigator assessment at maximum frown and at rest, independent reader assessment at maximum frown and at rest, and the subjects' assessment and satisfaction. Figure 10 illustrates the data as generated collectively, and broken into the two different treatment sites.

In summary, the data presented herein demonstrate that lyophilized MT10109 dosed at 20U demonstrates similarity to BOTOX® at early time points (e.g. day 30). Further, it is demonstrated that MT10109 dosed at 20U displays an increased sustained effect compared to BOTOX®, as the response of treatment was seen to be increased in the MT10109 20U group compared to BOTOX® 20U group at 120 days post treatment.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art

without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations

WE CLAIM:

1. A method for treating a condition in a patient in need thereof, the method comprising the step of locally administering a therapeutically effective amount of an animal-protein-free botulinum toxin composition, whereby a symptom of the condition is thereby effectively alleviated for a period of time longer than that of an animal-protein-containing botulinum toxin composition.

2. The method of claim 1, wherein the animal-protein-free botulinum toxin composition is in a form selected from the group consisting of a liquid composition and a lyophilized composition.

3. The method of claim 2, wherein the liquid composition comprises botulinum toxin, polysorbate 20, and methionine.

4. The method of claim 2, wherein the lyophilized composition comprises botulinum toxin, polysorbate, and methionine, and one or more components selected from the group consisting of a sugar, a sugar alcohol, and an ionic compound.

5. The method of claim 1, wherein the botulinum toxin is selected from a group consisting of botulinum toxin serotypes A, B, C, D, E, F, and G.

6. The method of claim 1, wherein the animal-protein-free botulinum toxin composition persists in the patient for a period longer than that of an animal-protein-containing botulinum toxin composition.

7. The method of claim 1, wherein the condition is selected from the group consisting of glabellar lines, marionette lines, brow furrows, lateral canthal lines, and any combinations thereof.

8. The method of claim 1, wherein the effective alleviation of a symptom of the condition is the temporary improvement in appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity.

9. The method of claim 8, wherein the animal-protein-free composition provides effective alleviation for a period of time of at least 16 weeks.

10. The method of claim 1, wherein the effective alleviation of a symptom of the condition is the temporary improvement in appearance of moderate to severe lateral canthal lines associated with orbicularis oculi muscle activity.

11. The method of claim 10, wherein the animal-protein-free composition provides effective alleviation for a period of time of at least 16 weeks.

12. The method of claim 1, wherein the effective alleviation of a symptom of the condition is the reduction of severity of abnormal head position and neck pain associated with cervical dystonia.

13. The method of claim 12, wherein the animal-protein-free composition provides effective alleviation for a period of time of at least 16 weeks.

14. The method of claim 1, wherein the effective alleviation of a symptom of the condition is the prophylaxis of headaches in patients with migraine.

15. The method of claim 14, wherein the animal-protein-free composition provides effective alleviation for a period of time of at least 16 weeks.

16. The method of claim 1, wherein the effective alleviation of a symptom of the condition is the treatment of depression.

17. The method of claim 1, wherein the effective alleviation of a symptom of the condition is an improvement in a depression rating scale selected from the group consisting of Beck Depression Inventory, Hamilton Rating Scale for Depression, Clinical Global Impression, Hospital Anxiety and Depression Scale, and Montgomery-Asberg Depression Rating Scale.

18. The method of claim 16, wherein the animal-protein-free composition provides effective alleviation for a period of time of at least 16 weeks.

19. The method of claim 1, wherein the condition is selected from the group consisting of detrusor overactivity associated with a neurologic condition, chronic migraine, upper limb spasticity, cervical dystonia, primary axillary hyperhidrosis, blepharospasm and strabismus, idiopathic overactive bladder, and any combinations thereof.

20. A method for treating a condition in a patient in need thereof, the method comprising the step of locally administering a therapeutically effective amount of an animal-protein-free botulinum toxin composition, wherein the composition is administered at an interval of time between a first treatment and a second treatment effective to maintain alleviation of at least one symptom of the condition, that is greater than the interval of time for an animal-protein-containing botulinum toxin composition dosed at the same amount and administered in the same manner and to the same location(s) as that of the animal-protein-free composition.

21. The method of claim 20, wherein the animal-protein-free botulinum toxin composition is in a form selected from the group consisting of a liquid pharmaceutical composition and a pharmaceutical lyophilized preparation.

22. The method of claim 21, wherein the liquid pharmaceutical composition comprises botulinum toxin, polysorbate 20, and methionine.

23. The method of claim 10, wherein the pharmaceutical lyophilized preparation comprises botulinum toxin, polysorbate, and methionine, and one or more components selected from the group consisting of a sugar, a sugar alcohol, and an ionic compound.

24. The method of claim 20, wherein the botulinum toxin is selected from a group consisting of botulinum toxin serotypes A, B, C, D, E, F, and G.

25. The method of claim 20, wherein the interval of time between a first treatment and a second treatment is greater than 3 months.

26. The method of claim 20, wherein the condition is selected from the group consisting of glabellar lines, marionette lines, crows feet, brow furrows, lateral canthal lines, and any combinations thereof.

27. The method of claim 20, wherein the condition is selected from the group consisting of detrusor overactivity associated with a neurologic condition, chronic migraine, upper limb spasticity, cervical dystonia, primary axillary hyperhidrosis, blepharospasm and strabismus, idiopathic overactive bladder, and any combinations thereof.

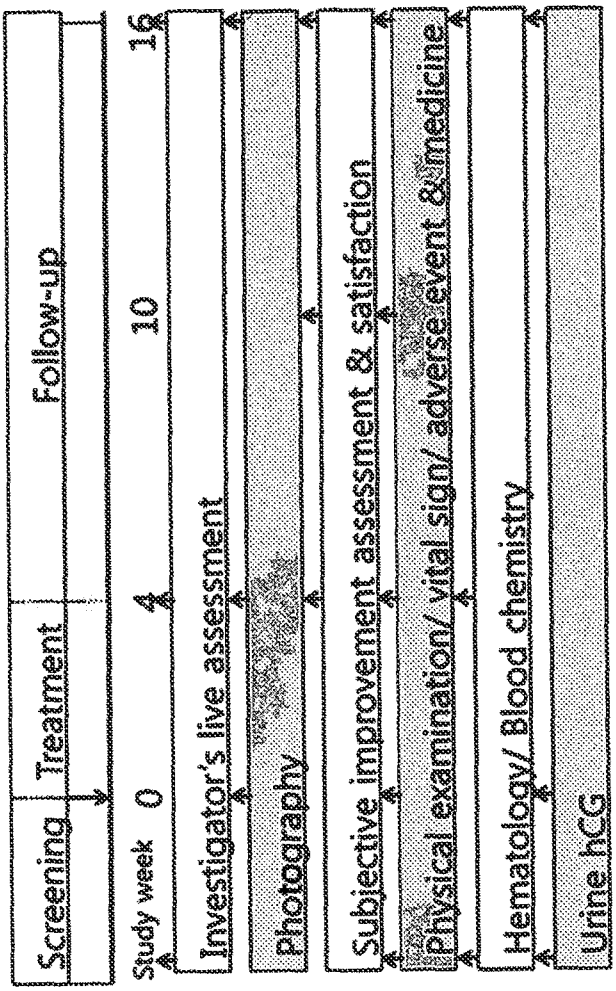

Screening
Treatment
Follow-up
Study week 0 4 10 16
Investigator's live assessment
Photography
Subjective improvement assessment & satisfaction
Physical examination/ vital sign/ adverse event &medicine
Hematology/ Blood chemistry
Urine hCG

Figure 1

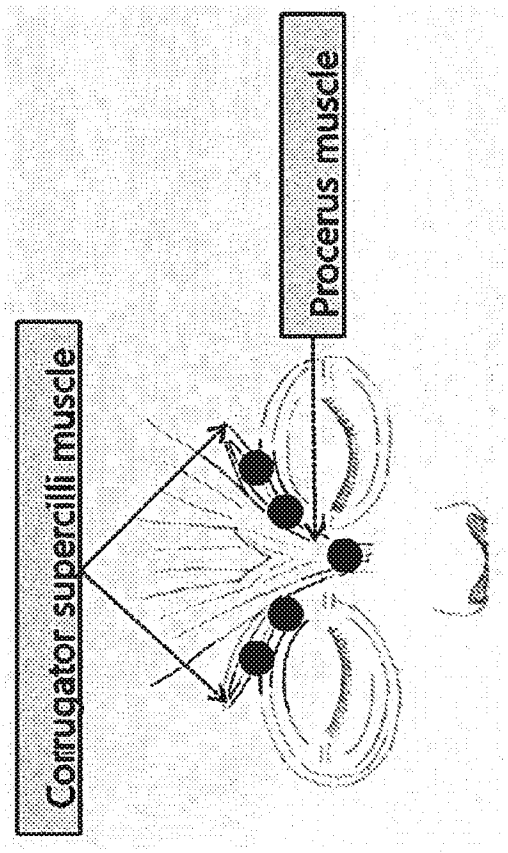


Figure 2

Figure 3B

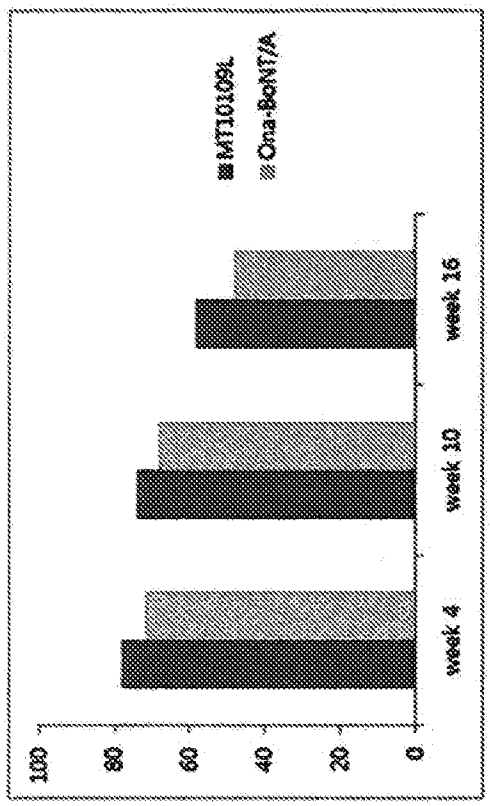


Figure 3A

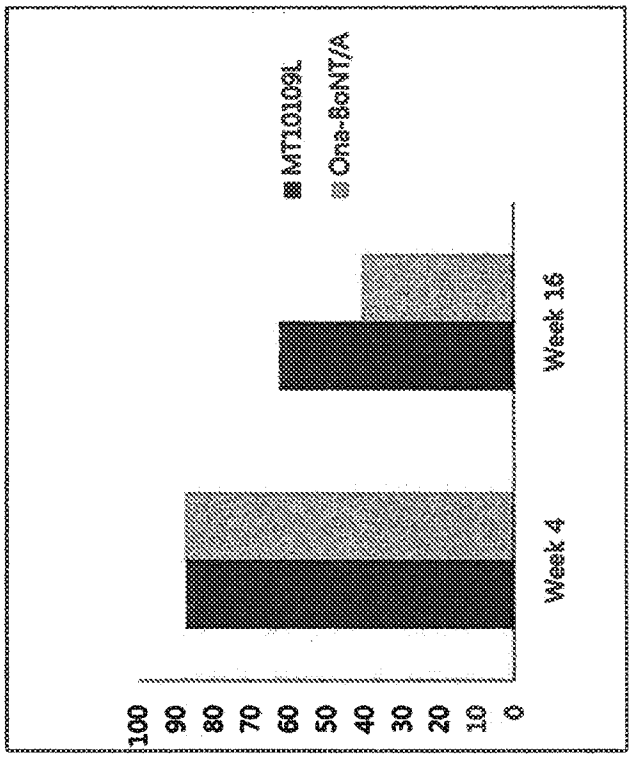


Figure 4A

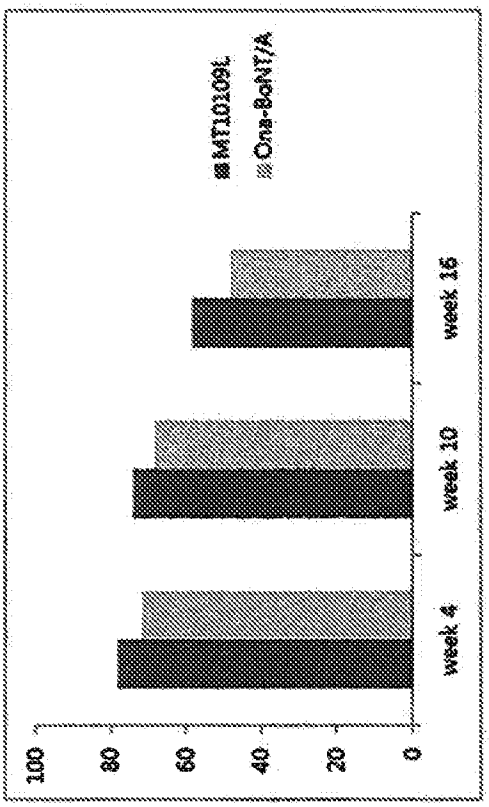
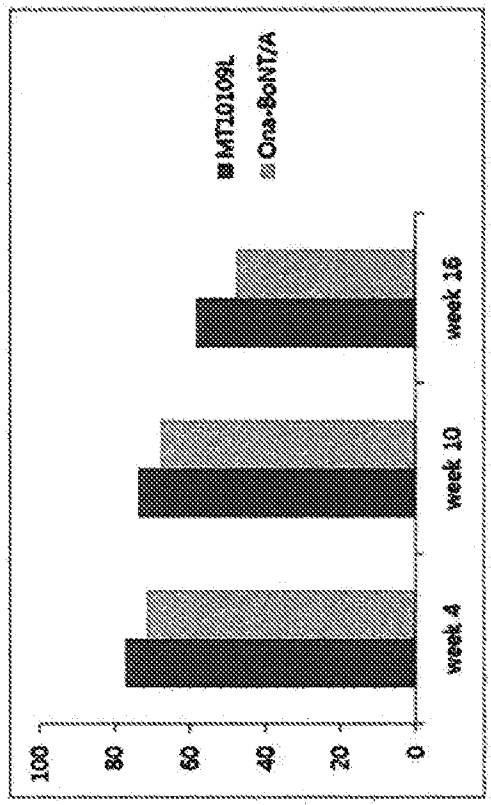


Figure 4B



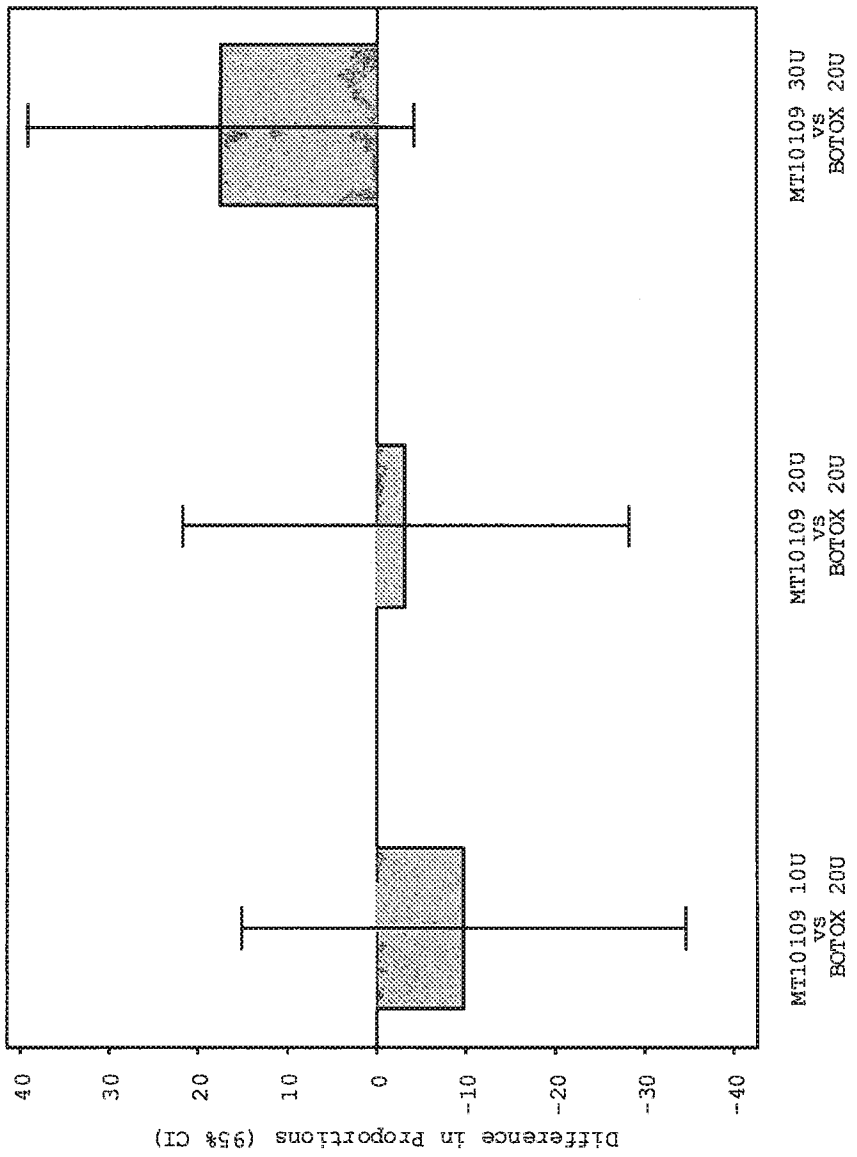
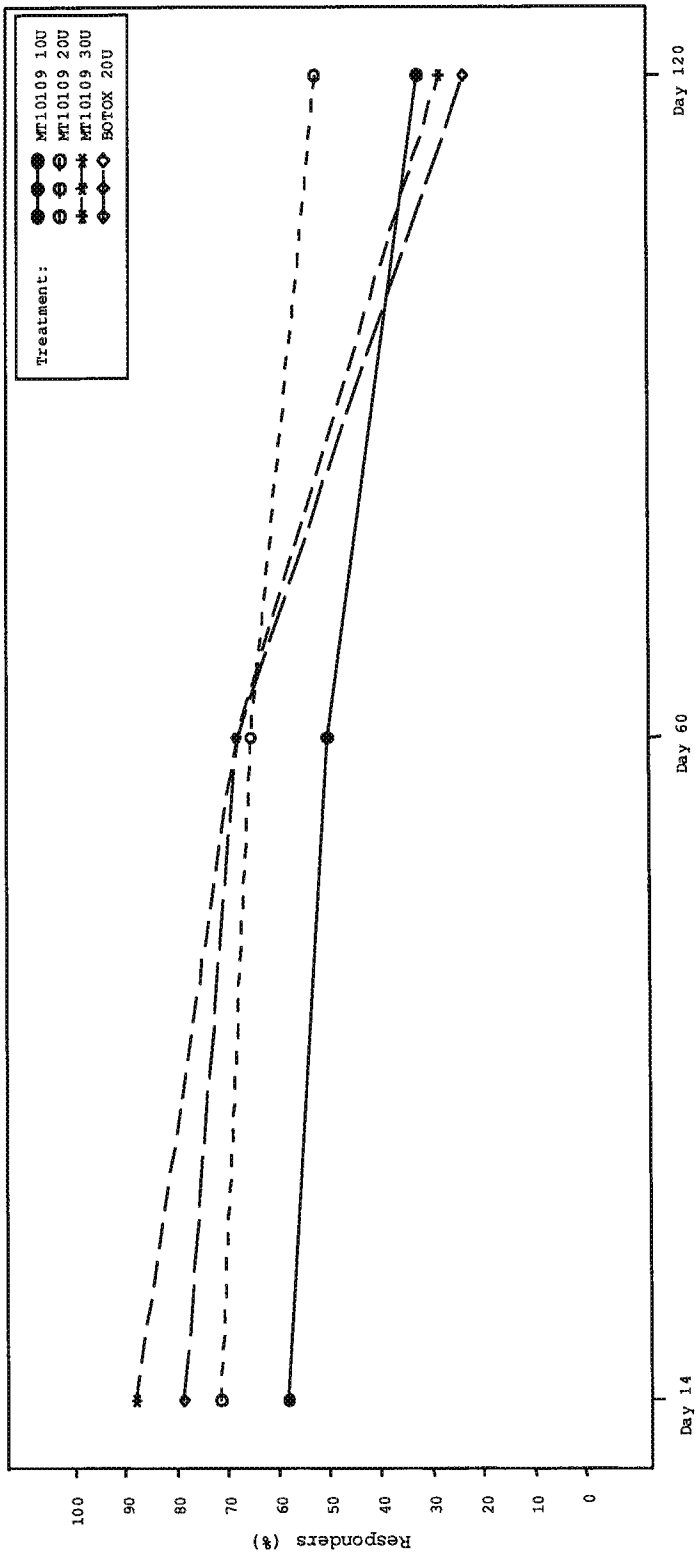


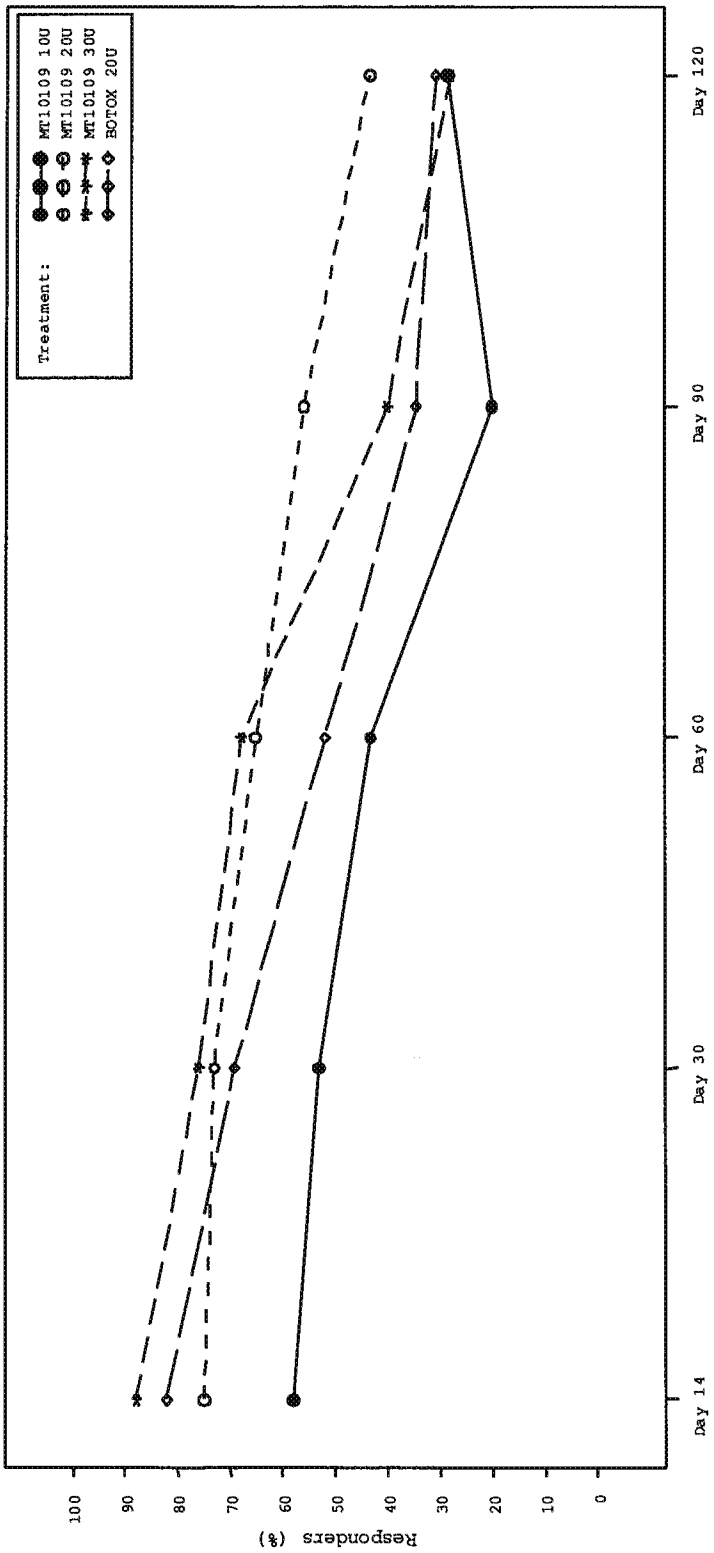
Figure 5

Abbreviations: CI=confidence interval; vs=versus.
Note: A responder was defined as having a glabellar line severity rating of none (0) or mild (1) at the corresponding post-baseline visit. The analysis was on imputed data using multiple imputation methodology. A Mantel-Haenszel chi-square test was used to compare treatments 2 by 2 and estimate the difference between the two treatments.



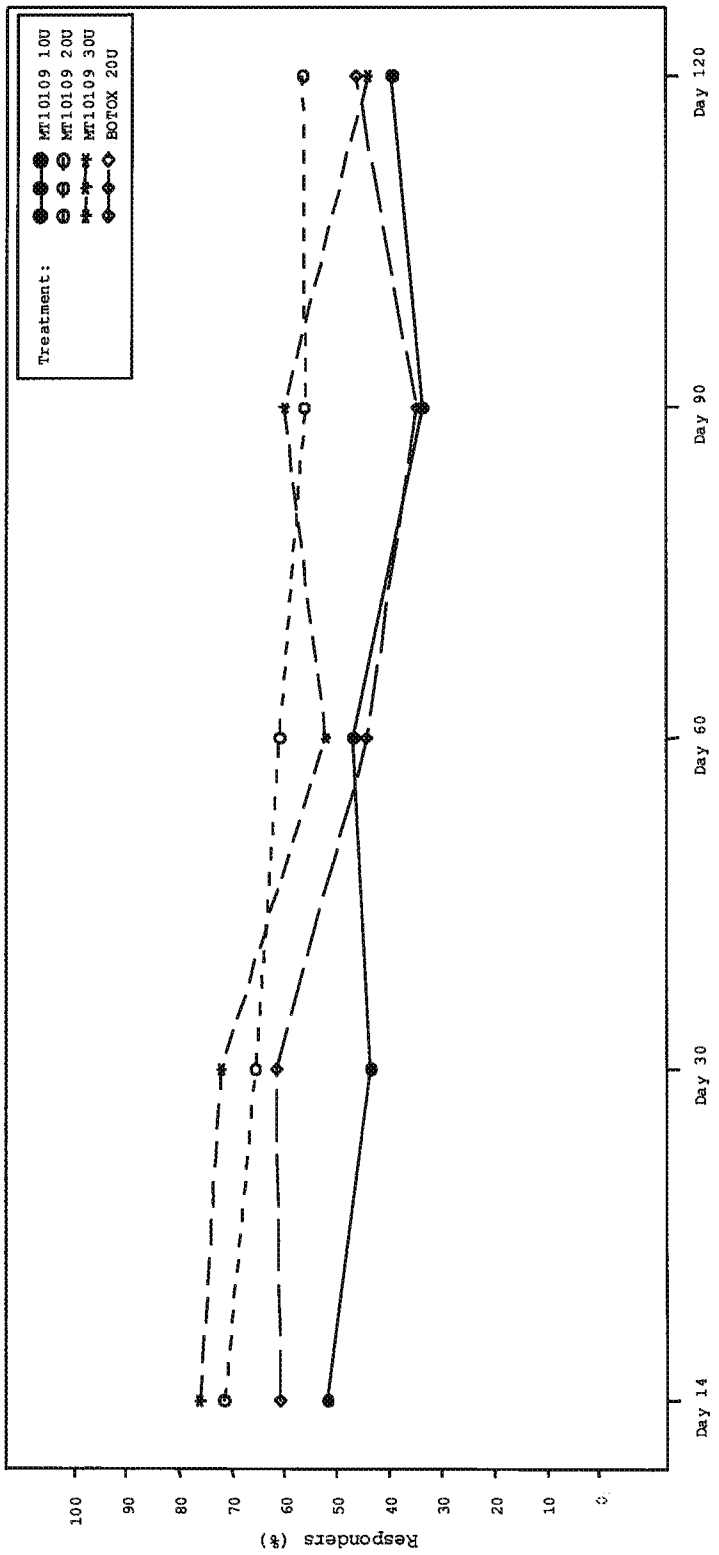
Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a severity rating of none (0) or mild (1) at the corresponding post-baseline visit.

Figure 6



Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least +2 (moderate improvement, i.e., about 50%) on the 9-point scale.

Figure 7



Note: Subjects included in the analysis had to have a baseline glabellar line severity rating of moderate (2) or severe (3). A responder was defined as having a score of at least 6 (satisfied) on the 7-point scale.

Figure 8

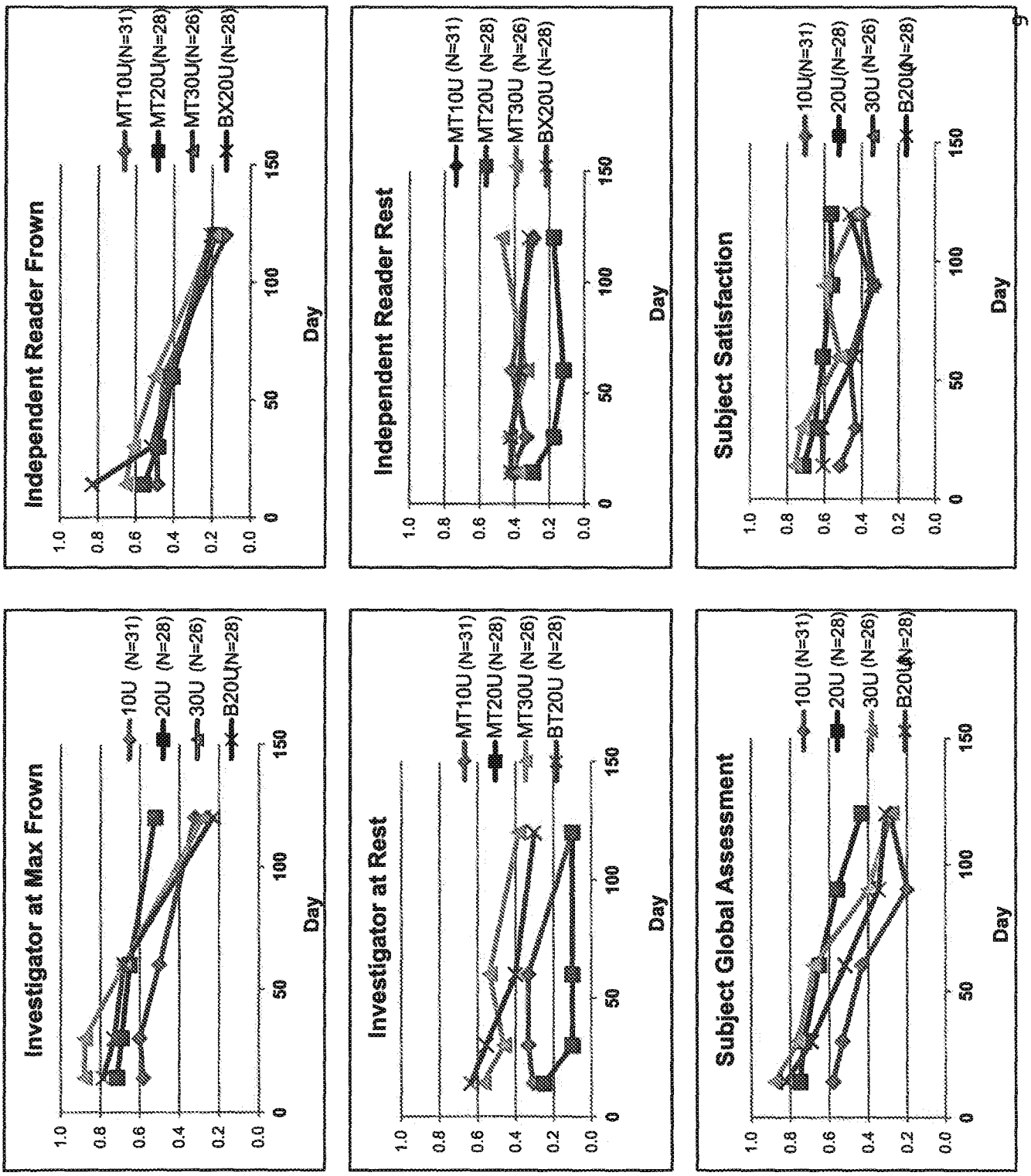
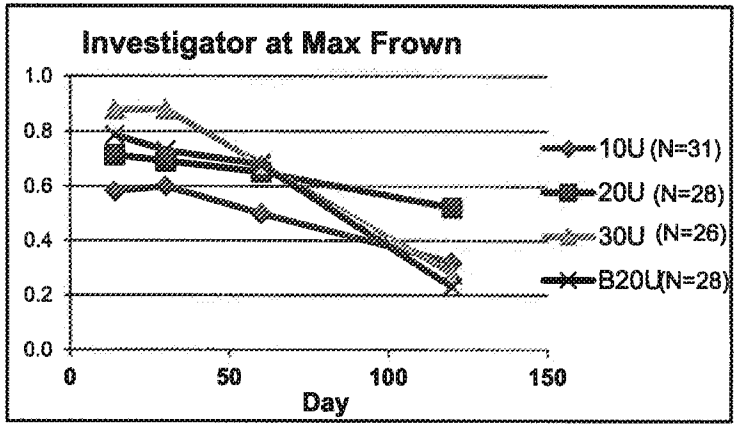

Primary time point D30
Glabellar Efficacy Results
Responder Analysis
Investigator at Max Frown
10U (N=31)
20U (N=28)
30U (N=26)
B20U(N=28)
Day
Independent Reader Frown
MT10U(N=31)
MT20U(N=28)
MT30U(N=26)
BX20U(N=28)
Day
Investigator at Rest
MT10U (N=31)
MT20U (N=28)
MT30U (N=26)
BT20U (N=28)
Day
Independent Reader Rest
MT10U (N=31)
MT20U (N=28)
MT30U (N=26)
BX20U (N=28)
Day
Subject Global Assessment
10U (N=31)
20U (N=28)
30U (N=26)
B20U(N=28)
Day
Subject Satisfaction
10U(N=31)
20U(N=28)
30U (N=26)
B20U(N=28)
Day

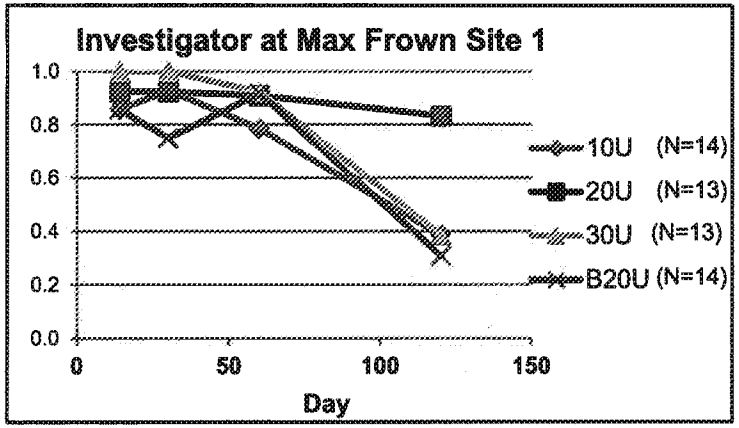
Figure 9

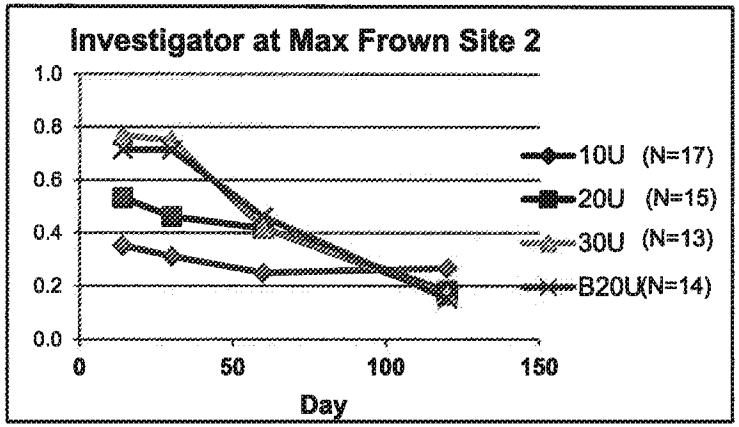
Glabellar Efficacy Results

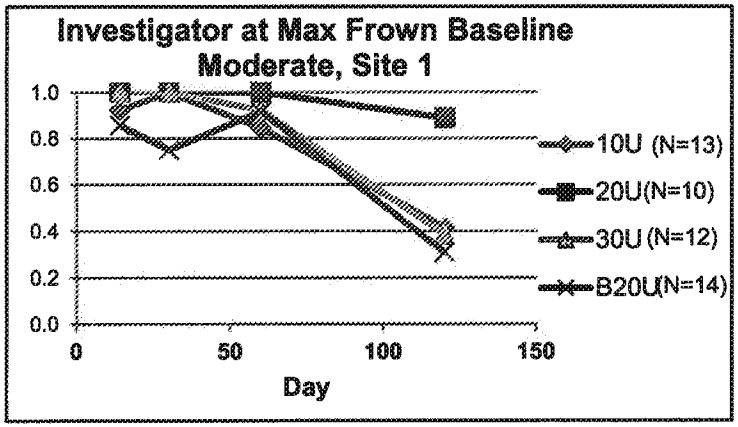
Responder Analysis

By Site









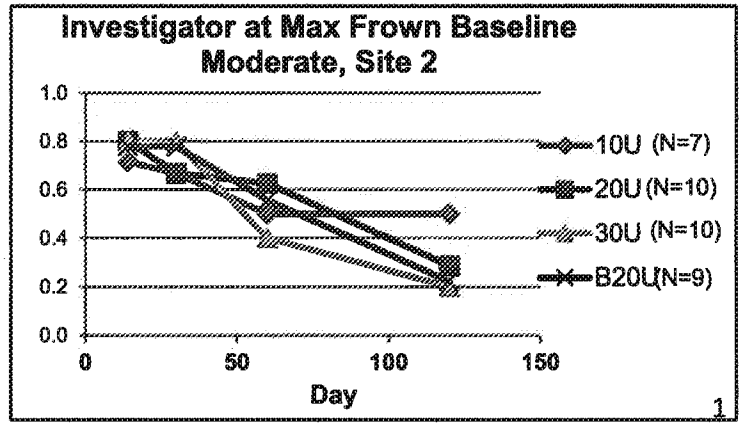


Figure 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/070113

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/48 A61K9/00 A61K9/19 A61P21/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP 2 692 350 A2 (MEDY TOX INC [KR]) 5 February 2014 (2014-02-05) paragraph [0006] - paragraph [0021] paragraph [0037]; claims 1-12	1,2,4-6, 12-15, 19-21,27
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2015	26/03/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Markopoulos, Eytyxia

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/070113

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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