corrugator, procerus, occipitalis, temporalis, trapezius, and cervical paraspinal muscle group. Doctors injecting the toxin may select additional muscles and areas to be injected in which patients particularly have pain in addition to fixed sites, a treatment strategy called "follow the pain" [https://www.botoxmedical.com/Common/Assets/APC55BL15%20Injection%20Workbook%20FINAL%20elec.pdf]. Each muscle and/or area affected by migraine typically has to be injected separately. As such, based on the diffusion characteristics of currently available toxin formulations, there is a limit to the total quantity of toxin that can be injected into the body at one time. While the treatment for migraine headaches involves regular intervention, which takes effect over a period of 4-7 days or longer after injection, the response to the treatment with botulinum toxin typically wears off a few weeks, often as early as week 10 before re-injection is scheduled at week 12, requiring the person suffering from migraine disease to be injected again.

SUMMARY

[0018] [0017a] In an aspect, there is provided the use of a dose of an injectable botulinum toxin composition to be administered using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve a therapeutic effect following treatment with the botulinum toxin composition, in the manufacture of a medicament for the treatment or reduction of frequency of headaches in an individual in need of treatment; wherein the botulinum toxin composition comprises a botulinum toxin component and pharmaceutically acceptable diluent suitable for injection; and wherein the total treatment dose of botulinum toxin component to be administered to the individual is 100 U to 450 U which is to be administered in one or more injections sites.In one of its examples, the disclosure relates to a method for treating or reducing the frequency and/or severity of headaches by administering by injection a dose of an injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group

consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites.

[0019] In some examples, the headache is selected from migraine headache, a post-traumatic headache, a post-craniotomy headache, tension-type headache, cluster headache, and/or medication-overuse headache. In preferred examples, the migraine headache is a chronic or an episodic migraine headache. For instance, in some examples, the migraine headache is an episodic migraine headache. In some examples, the headache is a high-frequency episodic migraine headache. In some examples, the migraine headache is a chronic migraine headache.

[0020] In some examples, the disclosure relates to a method for treating or reducing the frequency and/or severity of headaches by administering by injection a dose of an injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the composition further comprises a positively charged carrier comprising a positively charged backbone and at least one efficiency group; and wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites.

[0021] In an example, the botulinum toxin is present in the composition in a total dosage amount from more than 100 U, 100 to 200 U, 200 to 300 U, or 300-450 U. In an example, the botulinum toxin is present in the composition in a dosage amount selected from the group consisting of 100 U, 200U, 300U and 450U. In certain examples, the duration of the treatment effect (also referred to as the "efficacy window") can be greater than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; greater than 6 months; or at least 6 months through 10 months. In preferred examples the 150 kDa type A botulinum toxin form is used at these dosage amounts. In preferred examples daxibotulinumtoxin A is used at these dosage amounts.

[0022] In some examples, the positively charged backbone is polylysine or polyethyleneimine. In some examples, the positively charged backbone is a polylysine backbone wherein one or more positively charged efficiency groups are attached to said polylysine backbone. In some examples, the positively charged efficiency groups are either protected oligoarginine or TAT or modified TAT domains. In some examples, the positively charged efficiency groups are selected from an amino acid sequence selected from the group consisting of $(gly)_p$-RGRDDRRQRRR-$(gly)_q$ (SEQ ID NO: 1), $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO: 2), and $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO: 3), wherein the subscripts p and q are each independently an integer of from 0 to 20 and mixtures thereof. In preferred examples, the positively charged efficiency groups include the amino acid sequence RKKRRQRRR$(gly)_q$-$(K)_x$-$(gly)_p$-RKKRRQRRR, wherein

the subscript x is an integer from 5 to 50 or 10-30 or 10 to 20, wherein p and q are each an integer from 0 to 8. For instance, in a preferred example, the positively charged efficiency group has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4).

[0023] In a preferred example, the disclosure relates to a method for treating or reducing the frequency and/or the severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the composition further comprises a positively charged carrier comprising a positively charged backbone and at least one efficiency group; wherein the positively charged efficiency group has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4); wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites; and wherein the duration of the treatment effect comprises greater than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; or at least 6 months through 10 months.

[0024] In one of its examples, the disclosure relates to a method for treating or reducing the frequency and/or severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the injection sites correspond to one or more electrode placement sites selected from Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, Al, A2, T5, P3, P4, T6, 01, 02, Ground 1 (GND1), or Ground 2 (GND2) **(Table 1).** In some examples, the injection

sites further include muscle injection sites selected from trapezius or masseter. In some examples, the injection sites further correspond to one or more electrode placement sites selected from Cz, Pz, or Oz.

Table. 1 Injection Sites with EEG Detectable Brain Cortical Electrical Activity

Brain area	**Left**	**Midline**	**Right**
Frontal Pole (FP)	FP 1	Fpz	FP2
Frontal /Forehead (Ground)	GND1		GND2
Frontal (F)	F2		F2
Inferior Frontal (F)	F7		F8
Mid Temporal (T)	T7		T8
Posterior Temporal (P)	P7		P8
Central (C)	C3	Cz	C4
Parietal (P)	P3	Pz	P4
Occipital (O)	O1	Oz	O2
Mastoid/Ear/Auricular (A)	Al		A2

[0025] In some examples, the composition is administered at 10 to 25 injection sites, wherein 10 to 21 injection sites are EEG-associated injection sites and 2 to 4 injection sites are muscle injection sites; wherein the EEG-associated injection sites are selected from among Fpz, Fpl, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, Al, A2, T5, P3, P4, T6, O1, O2, GND1, and GND2, and the muscle injection sites are selected from right and left trapezius muscle and right and left masseter muscle. In preferred examples, the composition is administered at 17 injection sites; wherein the injection sites are Fp1, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, and Fpz. In preferred examples, the composition is administered at 17 EEG-associated injection sites and 2 muscle injection sites, wherein the 17 EEG-associated injection sites are Fpl, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, and the 2 muscle injection sites are the right and left trapezius muscle. In yet other examples, the composition is administered at 17 EEG-associated injection sites and 3 muscle injection sites, wherein the 17 EEG-

associated injection sites are Fpl, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, and the 3 muscle injection sites are the right and left trapezius muscle, and the right or left masseter muscle. In other examples, the composition is administered at 17 EEG-associated injection sites and 4 muscle injection sites, wherein the 17 EEG-associated injection sites are Fp1, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, and the 4 muscle injection sites are the right and left trapezius muscle and the right and left masseter muscle. In some examples, the injection sites further correspond to one or more electrode placement sites selected from Cz, Pz, or Oz. Identification of the injection location sites associated with EEG electrode placement sites, does not limit the practitioner from making additional injections without departing from this disclosure and would be within the scope of the disclosure disclosed herein.

[0026] In a preferred example, the disclosure relates to a method for treating or reducing the frequency and/or the severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the botulinum toxin is of serotype A; wherein the composition is administered at 10 to 25 injection sites, wherein 10 to 21 injection sites are EEG-associated injection sites and 2 to 4 injection sites are muscle injection sites; wherein the EEG-associated injection sites are selected from among Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, Al, A2, T5, P3, P4, T6, O1, O2, GND1, and GND2, and the muscle injection sites are selected from right and left trapezius muscle and right and left masseter muscle; wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites; and wherein the duration of the treatment effect comprises greater than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; or at least 6 months through 10 months.

[0027] In a preferred example, the disclosure relates to a method for treating or reducing the frequency and/or the severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect

following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the botulinum toxin is of serotype A; wherein the composition is administered to the injection sites consisting of Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, P3, P4, T6, O1, O2, GND1, GND2, trapezius muscles, and optionally masseter muscles; wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites; and wherein the duration of the treatment effect comprises greater than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; or at least 6 months through 10 months.

[0028] In a preferred example, the disclosure relates to a method for treating or reducing the frequency and/or the severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the botulinum toxin is of serotype A; wherein the composition further comprises a positively charged carrier comprising a positively charged backbone and at least one efficiency group; wherein the positively charged efficiency group has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4); wherein the composition is administered at 10 to 25 injection sites, wherein 10 to 21 injection sites are EEG-associated injection sites and 2 to 4 injection sites are muscle injection sites; wherein the EEG-associated injection sites are selected from among Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, A1, A2, T5, P3, P4, T6, O1, O2, GND1, and GND2, and the 2 to 4 muscle injection sites are selected from right and left trapezius muscle and right and left masseter muscle; wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites; and wherein the duration of the treatment effect comprises greater

than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; or at least 6 months through 10 months. In some examples, the injection sites further correspond to one or more electrode placement sites selected from Cz, Pz, or Oz.

[0029] In a preferred example, the disclosure relates to a method for treating or reducing the frequency and/or the severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the botulinum toxin is of serotype A; wherein the composition further comprises a positively charged carrier comprising a positively charged backbone and at least one efficiency group; wherein the positively charged efficiency group has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR (SEQ ID NO: 4); wherein the composition is administered to 17 EEG-associated injection sites and further 2 to 4 muscle injection sites, wherein the 17 EEG-associated injection sites are Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, P3, P4, T6, O1, O2, GND1, GND2, and the 2 to 4 muscle injection sites are the right and left trapezius muscle without administration to the masseter muscle (2 muscle sites), the right and left trapezius muscle with unilateral administration of the masseter (3 muscle sites), or the right and left trapezius with bilateral administration of masseter (4 muscle sites); wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites; and wherein the duration of the treatment effect comprises greater than 2 months; greater than 3 months; greater than 4 months; greater than 5 months; or at least 6 months through 10 months.

[0030] In some examples, the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U is administered in one or more injections sites. In some examples, the total treatment dose of botulinum toxin component is administered to the individual is 100 to 200U, 200 U to 300 U, or 300 U to 450 U, and 376 U, which is administered in one or more injections sites.

[0031] Modified injection techniques as described herein involve administration to allow for maximizing the dose while minimizing the number of injections required per site and thus maximizing the effect on cortical regions; while minimizing the side effects such as pain, swelling, muscle weakness, muscle paralysis, and muscle atrophy. In some examples, the treatment dose of botulinum toxin is administered using one or more injection techniques of interest, wherein the injection technique can be sleeving, angling, tunneling, single injection, or serial injection, or a modification thereof. In some examples, the composition is injected at T5, T6, O1, and O2; wherein the injection technique used is sleeving. In some examples, the composition is injected at T5, T6, O1, O2, FP1, FP2, F3, F4, P3, and P4; wherein the injection technique is sleeving. In some examples, the composition is injected at T3, T4, and in the trapezius muscle; wherein the injection technique is angling.

[0032] The methods described herein can deliver botulinum toxin in an effective amount for treating or preventing migraine disease and headaches generally. In some examples, the compositions are administered in a volume of about 100 µL to about 400 µL, about 100 µL to about 200 µL, about 200 µL to about 300 µL, about 300 µL to about 400 µL, about 100 µL; about 200 µL; about 300 µL, or about 400 µL; in preferred examples the injection volume is 100 µL, 200 µL or 400 µL.

[0033] In a further example, the disclosure relates to a combination therapy involving the administration of the injectable botulinum toxin composition as described herein in addition to one or more co-therapeutics. The one or more co-therapeutics can be administered separately, sequentially, or simultaneously with the injectable botulinum toxin composition, including in some examples, administration of the botulinum toxin composition together with the one or more co-therapeutics as a single injectable formulation. In some examples, the one or more co-therapeutics are administered near the end of the efficacy window of botulinum toxin, such as at about 1, 2, 3, or 4 weeks before the end of the treatment window. Efficacy window for botulinum toxin (i.e., the duration of action) can be from 12 weeks to 24 weeks, such as about 14 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, or 24 weeks. Thus, the one or more co-therapeutics can be administered at 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 weeks after a treatment with botulinum toxin.

[0034] Suitable co-therapeutics can be selected from an antagonist of calcitonin gene-related peptide (CGRP-antagonist), a 5-HT-1F receptor agonist, and an ergot compound.

Suitable CGRP-antagonists include both antibodies (and antigen-binding fragments thereof) and small molecule CGRP-antagonists. In some examples, the CGRP-antagonist is an anti-CGRP antibody or an antigen binding fragment thereof. Non-limiting examples include galcanezumab, fremanezumab, eptinezumab, erenumab, and combinations thereof Anti-CGRP antibodies or antigen binding fragments thereof can be administered with the botulinum toxin composition seperately, sequentially, or simultaneously. In some examples, the anti-CGRP antibody can be administered together with the botulinum toxin composition as a single injection at a suitable injection site as described further herein. In other examples, the anti-CGRP antibody can be administered separately from or sequentially with the botulinum toxin composition according to known methods of administering such antibodies.

[0035] In further examples, the CGRP-antagonist is a gepant. Non-limiting examples of suitable gepants include ubrogepant, rimegepant, atogepant, vazegepant, combinations thereof, and pharmaceutically-acceptable salts thereof. Such small molecule CGRP-antagonists can be administered separately, sequentially, or simultaneously with the injectable botulinum toxin composition. In some examples, the gepant can be administered at a suitable oral dose 1-3 times per day to an individual that is concurrently undergoing treatment with the injectable botulinum toxin composition. In further examples, the gepant can be administered together with the botulinum toxin composition as a single injectable dose.

[0036] In some examples, the combination therapeutic methods can be useful for any individual suffering from headaches such as migraines. In a further example, the individual receiving the combination therapy can be a non-responder or insufficient responder to one or more triptan drugs.

[0037] Another example of the present disclosure is a combination therapy involving the administration of the botulinum toxin composition with both a CGRP-antagonist and a 5-HT-1F receptor agonist. The three therapeutic agents can be administered separately, sequentially, or simultaneously, e.g., in some examples, in a single injection. In other examples, the individual in need of treatment can be administered the CGRP-antagonist and 5-HT-1F receptor agonist according to known routes of administration, separately from the botulinum toxin composition. Non-limiting examples of suitable 5-HT-1F receptor agonists include without limitation a ditan or a pharmaceutically-acceptable salt

thereof. The ditan, for example, can be lasmiditan or a pharmaceutically-acceptable salt thereof.

[0038] Similarly, another example of the present disclosure is a a combination therapy involving the administration of the botulinum toxin composition with both a CGRP-antagonist and an ergot compound. Suitable ergot compounds include ergotamine tartrate, ergonovine maleate, and ergoloid mesylates. Specific, non-limiting examples include dihydroergocornine, dihydroergocristine, dihydroergocryptine, and dihydroergotamine mesylate (DHE 45).

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] **FIG. 1** depicts electrode placement in the standard 10/20 System.

[0040] **FIG. 2** shows standard 10/20 system method of EEG electrode placement.

[0041] **FIG.** 3 shows injection locations based on the FTE ("follow the electrode") paradigm. Both frontal and rear/side views are shown. Each circle indicates an injection site. The size of the circle is representative of the botox distribution area achieved by use of special injection technique. Purple circles are mandatory injection sites, while pink circles are optional.

[0042] **FIG. 4** shows exemplary drug administration plan for patients.

[0043] Other examples, features and advantages of the disclosure will become apparent from the following detailed description and illustrative examples.

DETAILED DESCRIPTION

[0044] This invention relates to a method for treating or reducing the frequency and/or severity of headaches by administering by injection a dose of a sterile injectable botulinum toxin composition using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve the therapeutic effect following treatment with the botulinum toxin composition; wherein the botulinum toxin composition comprises a botulinum toxin component and a pharmaceutically acceptable diluent suitable for injection; and wherein the botulinum toxin component is selected from the group consisting of a botulinum toxin, a botulinum toxin complex, or a reduced botulinum toxin complex; wherein the total treatment dose of botulinum toxin component administered to the individual is 100 U to 450 U which is administered in one or more injections sites.

WHAT IS CLAIMED IS:

1. Use of

a dose of an injectable botulinum toxin composition to be administered using an injection paradigm that provides botulinum toxin at one or more locations of neuronal activity associated with EEG detectable brain cortical electrical activity in the individual to achieve a therapeutic effect following treatment with the botulinum toxin composition, in the manufacture of a medicament for the treatment or reduction of frequency of headaches in an individual in need of treatment;

wherein the botulinum toxin composition comprises a botulinum toxin component and pharmaceutically acceptable diluent suitable for injection;

and

wherein the total treatment dose of botulinum toxin component to be administered to the individual is 100 U to 450 U which is to be administered in one or more injections sites.

2. The use according to claim 1, wherein the headache is selected from migraine headache, a post-traumatic headache, a post-craniotomy headache, tension-type headache, cluster headache, and medication-overuse headache.
3. The use according to claim 2, wherein the migraine headache is a chronic or an episodic migraine headache.
4. The use according to claim 3, wherein the migraine headache is an episodic migraine headache.
5. The use according to claim 3, wherein the migraine headache is a chronic migraine headache.
6. The use according to claim 4, wherein the episodic migraine headache is a high-frequency episodic migraine.
7. The use according to claim 1, wherein the botulinum toxin is of a serotype selected from the group consisting of serotypes A, B, C, D, E, F, G, and mixtures thereof
8. The use according to claim 7, wherein the botulinum toxin is of serotype A having a molecular weight of 150 kDa.

9. The use according to claim 8, wherein the botulinum toxin A is daxibotulinumtoxin A.
10. The use according to any one of claims 1 to 9, wherein the composition further comprises a positively charged carrier comprising a positively charged backbone and at least one efficiency group.
11. The use according to claim 10, wherein the positively charged backbone is polylysine or polyethyleneimine.
12. The use according to claim 11, wherein the positively charged backbone is a polylysine backbone and wherein one or more positively charged efficiency groups are attached to said polylysine backbone.
13. The use according to claim 12, wherein the positively charged efficiency groups are either protected oligoarginine or TAT domains.
14. The use according to claim 13, wherein the positively charged efficiency groups are selected from an amino acid sequence selected from the group consisting of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO: 2), (gly)p-YGRKKRRQRRR-(gly)q (SEQ ID NO: 3), and (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO: 4), wherein the subscripts p and q are each independently an integer of from 0 to 20 and mixtures thereof
15. The use according to claim 14, wherein the positively charged efficiency groups include the amino acid sequence RKKRRQRRR-$(gly)_q$-(K)x-$(gly)_p$-RKKRRQRRR, wherein the subscript x is an integer from 5 to 50 or 10-30 or 10 to 20, wherein p and q are each an integer from 0 to 8.
16. The use according to claim 15, wherein the positively charged efficiency groups has the amino acid sequence RKKRRQRRRG-$(K)_{15}$-GRKKRRQRRR.
17. The use according to claim 12, wherein efficiency groups are bound at the C-terminus, the N-terminus or both.
18. The use according to claim 1, wherein the injection sites correspond to one or more electrode placement sites selected from Fpz, Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, Al, A2, P3, P4, T5, T6, O1, O2, GND1, or GND2.
19. The use according to claim 18, wherein the injection sites further include sites selected from trapezius muscle or masseter muscle.
20. The use according to claim 19, wherein the injection sites further correspond to one or more electrode placement sites selected from Cz, Oz, or Fz.

21. The use according to claim 20, wherein the composition is to be administered at 10 to 25 injection sites.
22. The use according to claim 21, wherein the composition is to be administered to the injection sites consisting of Fpl, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, and Fpz.
23. The use according to claim 21, wherein the composition is to be administered to the injection sites consisting of Fpl, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, and right and left trapezius muscle.
24. The use according to claim 21, wherein the composition is to be administered to the injection sites consisting of Fpl, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, trapezius muscles, and masseter muscles.
25. The use according to any one of claims 1 to 24, wherein the total treatment dose of botulinum toxin component to be administered to the individual is 100 U to 450 U which is to be administered in one or more injections sites.
26. The use according to any one of claims 1 to 24, wherein the total treatment dose of botulinum toxin component to be administered to the individual is 200 U to 300 U which is to be administered in one or more injections sites.
27. The use according to any one of claims 1 to 24, wherein the total treatment dose of botulinum toxin component to be administered to the individual is 300 U to 450 U which is to be administered in one or more injections sites.
28. The use according to claim 16, wherein the total treatment does of botulinum toxin component to be administered to the individual is 300 U to 450 U which is to be administered in one or more injection sites.
29. The use according to any of claims 22 to 24, wherein the total treatment dose of botulinum toxin component to the individual is 300 U to 450 U which is to be administered in one or more injection sites.
30. The use according to any one of claims 1 to 29, wherein the treatment dose of botulinum toxin is to be administered using one or more injection techniques of interest.
31. The use according to claim 30, wherein the injection technique is sleeving, angling, tunneling, single injection, or serial injection, or a modification thereof

32. The use according to any one of claims 1 to 31, wherein the injection volume for one injection site is from 100 to 400 µL.
33. The use according to any of claims 1 to 31, wherein the injection volume for one injection site is 100 µL.
34. The use according to any of claims 1 to 31, wherein the injection volume for one injection site is 200 µL.
35. The use according to any of claims 1 to 31, wherein the injection volume for one injection site is 300 µL.
36. The use according to any of claims 1 to 31, wherein the injection volume for one injection site is 400 µL.
37. The use according to any one of claims 9 to 17, wherein the duration of treatment effect comprises greater than 2 months, greater than 3 months, greater than 4 months, greater than 5 months, greater than 6 months, greater than 7 months, greater than 8 months, greater than 9 months, or at least 6 months through 10 months.
38. The use according to any one of the foregoing claims, further comprising one or more co-therapeutics selected from an antagonist of calcitonin gene-related peptide (CGRP-antagonist), 5-HT-IF receptor agonist and ergot compounds, to be administered to the individual.
39. The use according to claim 38, wherein the co-therpeutic is a CGRP antagonist and the CGRP-antagonist is an anti-calcitonin gene-related peptide receptor antibody (anti-CGRP antibody) or an antigen-binding fragment thereof
40. The use according to claim 39, wherein the anti-CGRP receptor antibody is selected from galcanezumab, fremanezumab, eptinezumab, erenumab, and combinations thereof
41. The use according to claim 39, wherein the CGRP-antagonist is a gepant.
42. The use according to claim 41, wherein the gepant is selected from ubrogepant, rimegepant, atogepant, vazegepant, combinations thereof, and pharmaceutically-acceptable salts thereof
43. The use according to claim 39, wherein the CGRP-antagonist is to be administered seperately, sequentially, or simultaneously with the injectable botulinum toxin composition.

44. The use according to any one of claim 38 to 43, wherein the individual is a non-responder or insufficient responder to one or more triptan drugs.

45. The use according to any one of claims 38 to 44, further comprising a 5-HT-1F receptor agonist to be administered.

46. The use according to claim 45, wherein the 5-HT-1F receptor agonist is a ditan or a pharmaceutically-acceptable salt thereof

47. The use according to claim 46, wherein the ditan is lasmiditan or a pharmaceutically-acceptable salt thereof

48. The use according to claim 45, wherein the injectable botulinum toxin composition, the CGRP-antagonist, and the 5-HT-1F receptor agonist are to be administered seperately, sequentially, or simultaneously.

49. The use according to any one of claims 38 to 48, further comprising an ergot compound to be administered.

50. The use according to claim 49, wherein the ergot compound is selected from ergotamine tartrate, ergonovine maleate, and ergoloid mesylates.

51. The use according to claim 49, wherein the ergot compound is selected from dihydroergocornine, dihydroergocristine, dihydroergocryptine, and dihydroergotamine mesylate (DHE 45).