

**WHAT IS CLAIMED IS:**

1. A method of treating or reducing frequency of headaches in an individual in need of treatment, the method comprising:

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 pharmaceutically acceptable diluent suitable for injection;

; 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.
2. The method 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 method according to claim 2, wherein the migraine headache is a chronic or an episodic migraine headache.
4. The method according to claim 3, wherein the migraine headache is an episodic migraine headache.
5. The method according to claim 3, wherein the migraine headache is a chronic migraine headache.
6. The method according to claim 4, wherein the episodic migraine headache is a high-frequency episodic migraine.
7. The method 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 method according to claim 7, wherein the botulinum toxin is of serotype A having a molecular weight of 150 kDa.

9. The method according to claim 8, wherein the botulinum toxin A is daxibotulinumtoxin A.
10. The method 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 method according to claim 10, wherein the positively charged backbone is polylysine or polyethyleneimine.
12. The method 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 method according to claim 12, wherein the positively charged efficiency groups are either protected oligoarginine or TAT domains.
14. The method according to claim 13, wherein the positively charged efficiency groups are selected from an amino acid sequence selected from the group consisting of (gly)<sub>p</sub>-RGRDDRRQRRR-(gly)<sub>q</sub> (SEQ ID NO: 2), (gly)<sub>p</sub>-YGRKKRRQRRR-(gly)<sub>q</sub> (SEQ ID NO: 3), and (gly)<sub>p</sub>-RKKRRQRRR-(gly)<sub>q</sub> (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 method according to claim 14, wherein the positively charged efficiency groups include the amino acid sequence RKKRRQRRR-(gly)<sub>q</sub>-(K)<sub>x</sub>-(gly)<sub>p</sub>-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 method according to claim 15, wherein the positively charged efficiency groups has the amino acid sequence RKKRRQRRRG-(K)<sub>15</sub>-GRKKRRQRRR.
17. The method according to claim 12, wherein efficiency groups are bound at the C-terminus, the N-terminus or both.
18. The method 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, A1, A2, P3, P4, T5, T6, O1, O2, GND1, or GND2.

19. The method according to claim 18, wherein the injection sites further include sites selected from trapezius muscle or masseter muscle.
20. The method 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 method according to claim 20, wherein the composition is administered at 10 to 25 injection sites.
22. The method according to claim 21, wherein the composition is administered to the injection sites consisting of Fp1, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, and Fpz.
23. The method according to claim 21, wherein the composition is administered to the injection sites consisting of Fp1, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, and right and left trapezius muscle.
24. The method according to claim 21, wherein the composition is administered to the injection sites consisting of Fp1, Fp2, T3, T4, T5, T6, O1, O2, F3, F4, P3, P4, F7, F8, GND1, GND2, Fpz, trapezius muscles, and masseter muscles.
25. The method according to any one of claims 1 to 24, 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.
26. The method according to any one of claims 1 to 24, wherein the total treatment dose of botulinum toxin component administered to the individual is 200 U to 300 U which is administered in one or more injections sites.
27. The method according to any one of claims 1 to 24, wherein the total treatment dose of botulinum toxin component administered to the individual is 300 U to 450 U which is administered in one or more injections sites.
28. The method according to claim 16, wherein the total treatment dose of botulinum toxin component administered to the individual is 300 U to 450 U which is administered in one or more injection sites.

29. The method 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 administered in one or more injection sites.
30. The method according to any one of claims 1 to 29, wherein the treatment dose of botulinum toxin is administered using one or more injection techniques of interest.
31. The method according to claim 30, wherein the injection technique is sleeving, angling, tunneling, single injection, or serial injection, or a modification thereof.
32. The method for use according to any one of claims 1 to 31, wherein the injection volume for one injection site is from 100 to 400  $\mu\text{L}$ .
33. The method for use according to any of claims 1 to 31, wherein the injection volume for one injection site is 100  $\mu\text{L}$ .
34. The method for use according to any of claims 1 to 31, wherein the injection volume for one injection site is 200  $\mu\text{L}$ .
35. The method for use according to any of claims 1 to 31, wherein the injection volume for one injection site is 300  $\mu\text{L}$ .
36. The method for use according to any of claims 1 to 31, wherein the injection volume for one injection site is 400  $\mu\text{L}$ .
37. The method for 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 method according to any one of the foregoing claims, further comprising administering to the individual one or more co-therapeutics selected from an antagonist of calcitonin gene-related peptide (CGRP-antagonist), 5-HT-IF receptor agonist and ergot compounds.
39. The method according to claim 38, wherein the co-therapeutic 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 method according to claim 39, wherein the anti-CGRP receptor antibody is selected from galcanezumab, fremanezumab, eptinezumab, erenumab, and combinations thereof.
41. The method according to claim 39, wherein the CGRP-antagonist is a gepant.
42. The method according to claim 41, wherein the gepant is selected from ubrogepant, rimegepant, atogepant, vazegepant, combinations thereof, and pharmaceutically-acceptable salts thereof.
43. The method according to claim 39, wherein the CGRP-antagonist is administered separately, sequentially, or simultaneously with the injectable botulinum toxin composition.
44. The method 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 method according to any one of claims 38 to 44, further comprising administering to the individual a 5-HT-1F receptor agonist.
46. The method according to claim 45, wherein the 5-HT-1F receptor agonist is a ditan or a pharmaceutically-acceptable salt thereof.
47. The method according to claim 46, wherein the ditan is lasmiditan or a pharmaceutically-acceptable salt thereof.
48. The method according to claim 45, wherein the injectable botulinum toxin composition, the CGRP-antagonist, and the 5-HT-1F receptor agonist are administered separately, sequentially, or simultaneously.
49. The method according to any one of claims 38 to 48, further comprising administering to the individual an ergot compound.
50. The method according to claim 49, wherein the ergot compound is selected from ergotamine tartrate, ergonovine maleate, and ergoloid mesylates.
51. The method according to claim 49, wherein the ergot compound is selected from dihydroergocornine, dihydroergocristine, dihydroergocryptine, and dihydroergotamine mesylate (DHE 45).