COMBINATION THERAPY OF LASMIDITAN AND A CGRP ANTAGONIST FOR USE IN THE TREATMENT OF MIGRAINE

The present invention relates to combinations of lasmiditan and a calcitonin gene-related peptide (CGRP) antagonist, for example the combination of galcanezumab and lasmiditan, and to methods of using the combinations for treatment of migraine, particularly migraine inadequately controlled by lasmiditan or a CGRP antagonist therapy alone, and more particularly, to treat therapy resistant migraine which is defined herein as migraine refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

The primary headache disorders, including migraine, are among the most common diseases and leading causes of disability worldwide. Migraine affects over 14% of adults worldwide. The available treatment options for migraine have unsatisfactory rates of efficacy, tolerability and patient adherence. In the 2013 Global Burden of Disease Study, migraine accounted for over half of all years lost to disability that were attributed to neurological disorders (*New strategies for the treatment and prevention of primary headache disorders*, N. M. Schuster & A. M. Rapoport, Nature Reviews Neurology (2016) 12, 635–650). Migraine is typically characterized by attacks of 1-3 days of severe headache, associated with nausea, vomiting, photo- and phonophobia (migraine without aura), and, in one third of patients, neurological aura symptoms (migraine with aura) (Goadsby, P.J. et al., New England Journal of Medicine 2002; 346: 257-270).

Lasmiditan, 2,4,6-trifluoro-N-[6-(1-methyl-piperidin-4-ylcarbonyl)-pyridin-2-yl]-benzamide (Compound I) is a selective and highly potent 5-HT-1F receptor agonist which is in development for treatment of migraine (See eg. *Lasmiditan for the Treatment of Migraine*, Capi, M. et al., Expert Opinion Investigational Drugs, (2017), Vol. 26, NO. 2, 227–234).

Calcitonin gene–related peptide (CGRP) is a 37-amino acid peptide found primarily in the C and Ad sensory fibers arising from the dorsal root and trigeminal ganglia, as well as the central nervous system. CGRP is a pain-signalling neuropeptide and potent vasodilator that is released from trigeminal sensory afferents and the spinal trigeminal nucleus. The role of CGRP in headache and migraine has been established in the art and a number of clinical studies are

currently evaluating the use of anti-CGRP antibodies for the treatment of headaches and migraine (See, for example, Dodick et al. Lancet Neurolology; 13(9): 885-892 (2014)).

Summary

In one aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of migraine in a patient.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient inadequately controlled by lasmiditan or a CGRP antagonist therapy alone.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab for the treatment of migraine in a patient inadequately controlled by lasmiditan or galcanezumab therapy alone.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient suffering from therapy resistant migraine wherein the patients migraines have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of migraine in a patient suffering from therapy resistant migraine wherein the patients migraines have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient inadequately controlled by lasmiditan or a CGRP antagonist therapy alone.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient inadequately controlled by lasmiditan or galcanezumab therapy alone.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient suffering from therapy resistant headaches wherein the patients headaches have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient suffering from therapy resistant headaches wherein the patients headaches have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once a day.

In another aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient,

wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once a day.

In a further aspect of the present disclosure, there is provided use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once a day.

Description

The present invention relates to combinations of lasmiditan and a calcitonin gene-related peptide (CGRP) antagonist, for example the combination of lasmiditan and galcanezumab, and to methods of using the combinations to treat migraine. More particularly, the present invention relates to the use of combinations of lasmiditan and a calcitonin gene-related peptide (CGRP) antagonist for the treatment of migraine inadequately controlled by lasmiditan or a CGRP antagonist therapy alone. More particularly, the present invention relates to the use of combinations of lasmiditan and a calcitonin gene-related peptide (CGRP) antagonist for the treatment of therapy resistant migraine which is defined herein as migraine refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

The management of patients with migraine is often unsatisfactory because available acute and preventive therapies are either ineffective or poorly tolerated. The acute treatment of migraine attacks has been limited to the use of analgesics, combinations of analgesics with caffeine, ergotamines, and the triptans. (For a description of such agents see e.g. *New Therapeutic Approaches for the Prevention and Treatment of Migraine*, Diener, H.C. et al., (2015) Lancet Neurololgy, 14:1010–22). Lasmiditan represents an innovative approach for acute migraine therapy by selectively targeting 5-HT-1F. While many patients will be able to successfully manage migraine episodes by treatment with lasmiditan or galcanezumab alone, a population of patients will fail to successfully manage their migraine attacks with either of these agents individually. These patients may have a number of migraine day's per-month that

continues to be significantly disabling. Further, some patients, referred to herein as therapy resistant migraine patients, will fail to successfully manage their migraine attacks and will suffer from migraines which are refractory to two or more prior monotherapy and/or dual therapy treatment regimens. As defined herein, therapy resistant migraine patients will be those that continue to suffer from 3 or more migraine days per month despite two or more prior monotherapy and/or dual therapy treatment regimens. As used herein, two or more prior monotherapy and/or dual therapy treatment regimens means prior unsatisfactory treatment attempts with a monotherapy or dual therapy regimen, such as triptans, ergotamines, nonsteroidal anti-inflammatory drugs (NSAIDs), nonnarcotic analgesics, and caffeine, either alone or two such agents in combination. Therapy resistant patients have yet to achieve substantial freedom

What is claimed:

1. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient.

2. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of migraine in a patient.

3. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient inadequately controlled by lasmiditan or a CGRP antagonist therapy alone.

4. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab for the treatment of migraine in a patient inadequately controlled by lasmiditan or galcanezumab therapy alone.

5. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of migraine in a patient suffering from therapy resistant migraine wherein the patients migraines have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

6. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of migraine in a patient suffering from therapy resistant migraine wherein the patients migraines have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

7. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

8. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

9. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

10. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

11. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

12. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

13. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once a day.

14. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once a day.

15. The use of any one of claims 2, 4, or 6, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once a day.

16. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient.

17. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient.

18. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient inadequately controlled by lasmiditan or a CGRP antagonist therapy alone.

19. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient inadequately controlled by lasmiditan or galcanezumab therapy alone.

20. Use of lasmiditan in simultaneous, separate, or sequential combination with a calcitonin gene-related peptide (CGRP) antagonist in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient suffering from therapy resistant headaches wherein the patients headaches have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

21. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the

group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient suffering from therapy resistant headaches wherein the patients headaches have been refractory to two or more prior monotherapy and/or dual therapy treatment regimens.

22. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

23. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

24. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered in an initial loading dose of 240 mg of followed by a monthly maintenance dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

25. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is

to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once or twice a day.

26. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once or twice a day.

27. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once or twice a day.

28. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 50 mg once a day.

29. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 100 mg once a day.

30. Use of lasmiditan in simultaneous, separate, or sequential combination with galcanezumab in the manufacture of a medicament for the treatment of a headache selected from the

group consisting of episodic headache, chronic headache, chronic cluster headache, or episodic cluster headache in a patient, wherein galcanezumab is to be administered at a monthly dose of 120 mg, and lasmiditan is to be administered at a dose of 200 mg once a day.

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