SUMMARY ~~OF THE INVENTION~~

In one aspect, the present disclosure pertains to a use of a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of refractory chronic cough (RCC) or idiopathic chronic cough (ICC).

One ~~aspect~~example of the ~~invention~~disclosure pertains to a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester (also referred to herein as “AX-8” or “Gly-O-iPr”), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, as described herein, for use in a method of treatment of the human or animal body by therapy, more specifically, for use in a method of treatment of chronic cough (CC), including, for example, refractory chronic cough (RCC) and idiopathic chronic cough (ICC), and as described herein.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to use a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester (also referred to herein as “AX-8” or “Gly-O-iPr”), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, as described herein, in the manufacture of a medicament for treatment, more specifically, for the treatment of chronic cough (CC), including, for example, refractory chronic cough (RCC) and idiopathic chronic cough (ICC), and as described herein.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a method of treatment, more specifically, a method of treatment of chronic cough (CC), including, for example, refractory chronic cough (RCC) and idiopathic chronic cough (ICC), and as described herein, comprising administering to a patient in need of treatment a therapeutically effective amount of a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester (also referred to herein as “AX-8” or “Gly-O-iPr”), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, as described herein, preferably in the form of a pharmaceutical composition.

Another ~~aspect~~example of the present ~~invention~~disclosure pertains to a kit comprising (a) a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester (also referred to herein as “AX-8” or “Gly-O-iPr”), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for its use, for example, written instructions on how to administer the compound for the treatment of chronic cough (CC), including, for

example, refractory chronic cough (RCC) and idiopathic chronic cough (ICC), and as described herein.

As will be appreciated by one of skill in the art, features and preferred ~~embodiment~~examples of one ~~aspect~~example of the ~~invention~~disclosure will also pertain to other ~~aspect~~examples of the ~~invention~~disclosure.

CLAIMS

~~1. A compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in a method of treatment of refractory chronic cough (RCC) or idiopathic chronic cough (ICC).~~

~~2~~1. Use of a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for the treatment of refractory chronic cough (RCC) or idiopathic chronic cough (ICC).

~~3. A method of treatment of refractory chronic cough (RCC) or idiopathic chronic cough (ICC)comprising administering to a patient in need of treatment a therapeutically effective amount of a compound that is [((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl)-amino]-acetic acid isopropyl ester, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.~~

~~4~~2. ~~A~~ The ~~compound according to claim 1,~~ use according to claim ~~2~~1~~, or a method according to claim 3~~, wherein:

the chronic cough is idiopathic chronic cough (ICC).

~~5~~3. The~~A compound according to claim 1,~~ use according to claim ~~2~~1~~, or a method according to claim 3~~, wherein:

the chronic cough is refractory chronic cough (RCC).

~~6~~4. The~~A compound according to claim 1,~~ use according to claim ~~2~~1~~, or a method according to claim 3~~, wherein:

the chronic cough is refractory chronic cough (RCC) that persists after assessment and treatment of a cough-related condition.

~~7.~~5. The~~A compound according to claim 1,~~ use according to claim ~~2~~1~~, or a method according to claim 3,~~ wherein:

the chronic cough is refractory chronic cough (RCC) that persists after assessment and treatment of: asthma, eosinophilic bronchitis, post-nasal drip syndrome (PNDS), gastro-oesophageal reflux disease (GORD), bronchiectasis chronic obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF).

~~8~~6. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with allotussia.

~~9~~7. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2 and 4~~ 1 to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with hypertussia.

~~10~~8. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with cough hypersensitivity syndrome (CHS).

~~11~~9. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with cough hypersensitivity reflex (CHR).

~~12~~10. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with laryngeal paraesthesia.

~~13~~11. The~~A~~ ~~compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is associated with laryngeal hypersensitivity syndrome (LHS).

~~14~~12. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough (ICC) is sensory neuropathic cough.

~~15~~13. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough is associated with peripheral sensitization; central sensitization (cough centre); and/or cortical and/or subcortical maladaptive plasticity.

~~16~~14. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough is associated with vagal neuropathy.

~~17~~15. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein::

the refractory chronic cough (RCC) or idiopathic chronic cough is associated with airway inflammation.

~~18~~16. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~5, ~~or a method according to any one of claims 3 and 4 to 7~~, wherein:

the refractory chronic cough (RCC) or idiopathic chronic cough is associated with neurogenic inflammation and/or neuroinflammation.

~~19~~17. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~16~~, or a method according to any one of claims 3 and 4 to 7~~, wherein:

the treatment is to reduce cough frequency;

the treatment is to reduce hourly cough frequency;

the treatment is to reduce median hourly cough frequency;

the treatment is to reduce mean hourly cough frequency;

the treatment is to reduce awake hourly cough frequency;

the treatment is to reduce awake median hourly cough frequency;

the treatment is to reduce awake mean hourly cough frequency;

the treatment is to reduce asleep hourly cough frequency;

the treatment is to reduce asleep median hourly cough frequency;

the treatment is to reduce asleep mean hourly cough frequency;

the treatment is to reduce cough severity;

the treatment is to reduce urge-to-cough; and/or

the treatment is to reduce throat irritation.

~~20~~18. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~17~~, or a method according to any one of claims 3 and 4 to 7~~, wherein:

the treatment is by topical oral administration of the compound;

the treatment is by topical oromucosal administration of the compound;

the treatment is by topical buccal administration of the compound;

the treatment is by topical sublingual administration of the compound;

the treatment is by topical intranasal administration of the compound; or

the treatment is by topical transmucosal administration of the compound.

~~21~~19. The~~A compound according to any one of claims 1 and 4 to 7,~~ use according to any one of claims ~~2~~ 1 ~~and 4~~ to ~~7~~18~~, or a method according to any one of claims 3 and 4 to 7~~, wherein:

the treatment is with a dose in the range of from ~~about~~ 1 µg to ~~about~~ 5 mg of the compound per kilogram body weight of the subject per day;

the treatment is with a dose in the range of from ~~about~~ 5 µg to ~~about~~ 2 mg of the compound per kilogram body weight of the subject per day;

the treatment is with a dose in the range of from ~~about~~ 15 µg to ~~about~~ 0.7 mg of the compound per kilogram body weight of the subject per day;

the treatment is with a dose in the range of from ~~about~~ 30 µg to ~~about~~ 0.4 mg of the compound per kilogram body weight of the subject per day; or

the treatment is with a dose in the range of from ~~about~~ 70 µg to ~~about~~ 0.3 mg of the compound per kilogram body weight of the subject per day.

2220. TheA compound according to any one of claims 1 and 4 to 7, use according to any one of claims 2 1 and 4 to 718, or a method according to any one of claims 3 and 4 to 7, wherein:

the treatment is with a dose in the range of from about 0.07 mg to about 350 mg of the compound per day;

the treatment is with a dose in the range of from about 0.35 mg to about 140 mg of the compound per day;

the treatment is with a dose in the range of from about 1 mg to about 50 mg of the compound per day;

the treatment is with a dose in the range of from about 2 mg to about 30 mg of the compound per day; or

the treatment is with a dose in the range of from about 5 mg to about 20 mg of the compound per day.

2321. TheA compound according to any one of claims 1 and 4 to 7, use according to any one of claims 2 1 and 4 to 720, or a method according to any one of claims 3 and 4 to 7, wherein:

the treatment is by a treatment regimen of 1 to 5 administrations daily;

the treatment is by a treatment regimen of 1 to 4 administrations daily;

the treatment is by a treatment regimen of 2 to 5 administrations daily;

the treatment is by a treatment regimen of 2 to 4 administrations daily;

the treatment is by a treatment regimen of 2 administrations daily;

the treatment is by a treatment regimen of 3 administrations daily; or

the treatment is by a treatment regimen of 4 administrations daily.

2422. TheA compound according to any one of claims 1 and 4 to 7, use according to any one of claims 2 1 and 4 to 721, or a method according to any one of claims 3 and 4 to 7, wherein:

the treatment is by a *pro re nata* (PRN) treatment regimen.

2523. TheA compound according to any one of claims 1 and 4 to 7, use according to any one of claims 2 1 and 4 to 722, or a method according to any one of claims 3 and 4 to 7, wherein:

the compound is formulated as a tablet;

the compound is formulated as an orally disintegrating tablet (ODT);

the compound is formulated as a spray;

the compound is formulated as a mist; or

the compound is formulated as an aerosol.