(*e.g.*, degenerative joint disease), throat conditions (*e.g.*, dysphagia or spasmodic dysphonias), tactile sensitivity, electrolyte imbalance and/or vitamin deficiency, respiratory conditions (*e.g.*, asthma), cough, and sarcoidosis. As shown herein, compositions that include activators of ion channels (*e.g.*, TRP or ASIC channels) may be useful to treat the above-mentioned conditions.

SUMMARY OF THE INVENTION

In one aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient for the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis or multiple sclerosis in a subject, wherein said composition is a liquid or solid, wherein said composition is formulated for oral administration and wherein said composition is formulated for delayed release of said ion channel activator. In an embodiment, the present disclosure features a composition formulated for oral administration, said composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof). In some embodiments, the composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, the composition further comprises a pharmaceutically acceptable excipient. In some embodiments, the composition further comprises a plurality of pharmaceutically acceptable excipients.

In some embodiments, the composition is formulated for modified release (e.g., delayed release, extended release, or rapid release) of said ion channel activator (e.g., TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof). In some embodiments, said pharmaceutically acceptable excipient comprises an agent for modified release (e.g., delayed release, extended release, or rapid release) of an ion channel activator (e.g., a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), such that, when orally administered to a subject, the ion channel activator (e.g., TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof) is not substantially released in the stomach of said subject. In some embodiments, the agent for modified release (e.g., delayed release, extended release, or rapid release) is selected from the group consisting of: hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, and mixtures thereof.

In some embodiments, said pharmaceutically acceptable excipient comprises a coating. In some embodiments, said coating is selected from the group consisting of: enteric coatings, sugar coatings, and polymeric coatings. In some embodiments, said ion channel activator (*e.g.*, TRPV1

mg, about 500 mg, about 750 mg, about 1 g, about 2 g, about 5 g, about 10 g, or more. In some embodiments, an effective amount of the solid formulation is between about 0.5 mg and about 100 mg. In some embodiments, an effective amount of the solid formulation is between about 100 mg and about 500 mg. In some embodiments, an effective amount of the solid formulation is between about 500 mg and about 1000 mg.

In some embodiments, the composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) is formulated for use once a day. In some embodiments, the composition is formulated for use at least about 1 time per day, about 2 times per day, about 3 times per day, about 4 times per day, about 5 times per day, or more. In some embodiments, the composition is formulated for use about 1-3 times per day. In some embodiments, the composition is formulated for use for a period of about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient for the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis or multiple sclerosis in a subject in need thereof, wherein upon administration, the ion channel activator has a residence time of greater than about 5 seconds in the mouth of the subject and wherein the composition is formulated for oral administration. In an embodiment, the disclosure features a composition formulated for oral administration, said composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a pharmaceutically acceptable excipient, wherein said composition is a liquid or solid, and wherein said composition is formulated for delayed release of said ion channel activator (*e.g.*, TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof). In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof), and a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel

activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In some embodiments, said pharmaceutically acceptable excipient comprises an agent for delayed release of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), such that, when orally

What is claimed is:

1. The use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient, for the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis or multiple sclerosis in a subject in need thereof, wherein said composition is a liquid or solid, wherein said composition is formulated for oral administration, and wherein said composition is formulated for delayed release of said ion channel activator.

2. The use of claim 1, wherein said composition comprises a plurality of ion channel activators and a pharmaceutically acceptable excipient.

3. The use of claims 1 and 2, wherein said composition comprises two ion channel activators and a pharmaceutically acceptable excipient.

4. The use of any one of claims 1-3, wherein said composition comprises an ion channel activator and a plurality of pharmaceutically acceptable excipients.

5. The use of any one of claims 1-4, wherein said pharmaceutically acceptable excipient comprises an agent for delayed release of an ion channel activator such that, when orally administered to a subject, the ion channel activator is not substantially released in the stomach of said subject.

6. The use of claim 5, wherein the agent for delayed release is selected from the group consisting of: hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, and mixtures thereof.

7. The use of any one of claims 1-6, wherein said pharmaceutically acceptable excipient comprises a coating.

8. The use of claim 7, wherein said coating is selected from the group consisting of: enteric coatings, sugar coatings, and polymeric coatings.

9. The use of any one of claims 1-8, wherein said ion channel activator is embedded in biodegradable microparticles or nanoparticles for sustained release.

10. The use of any one of claims 1-9, wherein said composition further comprises a formulation base.

11. The use of claim 10, wherein said formulation base comprises an oil and a lipophilic additive.

12. The use of claim 12, wherein said oil is selected from the group consisting of: vegetable oil, mineral oil, soya oil, sunflower oil, corn oil, olive oil, nut oil, and liquid paraffin.

13. The use of claim 12, wherein said lipophilic additive is selected from the group consisting of: polyethylene glycol, fatty acid mono-, di-, or triglycerides, palmitic acid, stearic acid, behenic acid, polyethylene glycol fatty acid esters, candelilla wax, carnauba wax, polyethylene oxide wax, and petroleum wax.

14. The use of any one of claims 1-13, wherein the composition further comprises a coloring agent, a dissolving agent, a flavoring agent, a sweetener, a viscosity modifier, an electrolyte, a vitamin, a mineral, an antioxidant, or a preservative.

15. The use of any one of claims 1-14, wherein said composition is formulated as a liquid.

16. The use of claim 15, wherein said liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups, linctuses, drops, sprays, and elixirs.

17. The use of any one of claims 1-14, wherein said composition is formulated as a solid.

18. The use of claim 17, wherein said solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges, gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations.

19. The use of claim 18, wherein said capsule is a hard or soft capsule.

20. The use of any one of claims 1-19, wherein the ion channel activator comprises a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or a combination thereof.

21. The use of claim 20, wherein said TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

22. The use of claim 21, wherein said capsaicinoid is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

23. The use of claim 20, wherein said TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, methyl salicylate, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid.

24. The use of claim 20, wherein said ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid.

25. The use of any one of claims 20-24, wherein said TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or a combination thereof is present from about 0.001% to about 10% (w/w) or about 0.001% to about 10% (v/v).

26. The use of any one of claims 1-25, wherein said composition is capable of reducing gastrointestinal side effects.

27. The use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient for the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis or multiple sclerosis in a subject in need thereof, wherein upon administration, the ion channel activator has a residence time of greater than about 5 seconds in the mouth of the subject and wherein the composition is formulated for oral administration.

28. The use of claim 27, wherein said composition comprises a plurality of ion channel activators.

29. The use of any one of claims 27-28, wherein said composition comprises two ion channel activators.

30. The use of any one of claims 27-29, wherein said composition comprises an ion channel activator and a plurality of pharmaceutically acceptable excipients.

31. The use of any one of claims 27-30, wherein said ion channel activator has a residence time of greater than about 60 seconds in the mouth of a subject.

32. The use of any one of claims 27-31, wherein said composition further comprises a formulation base.

33. The use of claim 32, wherein said formulation base comprises an oil and a lipophilic additive.

34. The use of claim 33, wherein said oil is selected from the group consisting of: vegetable oil, mineral oil, soya oil, sunflower oil, corn oil, olive oil, nut oil, and liquid paraffin.

35. The use of claim 33, wherein said lipophilic additive is selected from the group consisting of: polyethylene glycol, fatty acid mono-, di-, or triglycerides, palmitic acid, stearic acid, behenic acid, polyethylene glycol fatty acid esters, candelilla wax, carnauba wax, polyethylene oxide wax, and petroleum wax.

36. The use of any one of claims 27-35, wherein the composition further comprises a coloring agent, a dissolving agent, a flavoring agent, a sweetener, a viscosity modifier, an electrolyte, a vitamin, a mineral, an antioxidant, or a preservative.

37. The use of any one of claims 27-36, wherein said composition is formulated as a liquid.

38. The use of claim 37, wherein said liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups, linctuses, drops, sprays, and elixirs

39. The use of any one of claims 27-36, wherein said composition is formulated as a solid.

40. The use of claim 39, wherein said solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges, gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations.

41. The use of claim 40, wherein said capsule is a hard or soft capsule.

42. The use of any one of claims 27-41, wherein the ion channel activator comprises a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or a combination thereof.

43. The use of claim 42, wherein said TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

44. The use of claim 43, wherein said capsaicinoid is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

45. The use of claim 42, wherein said TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, methyl salicylate, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid.

46. The use of claim 42, wherein said ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid.

47. The use of any one of claims 27-46, wherein said TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or a combination thereof is present from about 0.001% to about 10% (w/w) or about 0.001% to about 10% (v/v).

48. The use of any one of claims 27-47, wherein said ion channel activator is to be ingested by the subject.

49. The use of any one of claims 27-48, wherein said ion channel activator is to be held in the mouth by the subject.

50. The use of any one of claims 27-49, wherein said ion channel activator is to be dissolved in the mouth of the subject or chewed by the subject prior to swallowing.