Life Science 87: 36-41 (2010), and Casale et al, Ann Allergy Asthma Immunol 107: 364-370 (2011).

WO-A-2001/064280 discloses methods and devices for transcutaneous and transmucosal applications of carbon dioxide in the form of a gas and in the form of a capnic solution (such as carbonated water) for the relief of pain, including musculoskeletal disorders, neuralgias, rhinitis and other ailments.

US-A-2011/0046546 discloses apparatus, methods and kits for treating symptoms associated with common ailments, such as headaches, rhinitis, asthma, epilepsy, nervous disorders and the like.

The present inventors have recognized that the administration of a combination of a therapeutic substance, and control of pH, the intranasal gas pressure and/or NO concentration, such as by way of delivery of a gas through the nasal airway, can provide for an improved therapeutic treatment. In one embodiment control of pH, the intranasal gas pressure and/or NO concentration can provide for parasympathetic stimulation, which can provide for an additive effect or a synergistic effect, mediating uptake of a delivered therapeutic substance. In one example, a rapid onset of action of the therapeutic substance can be achieved.

In one aspect, the present disclosure provides a use of a therapeutic amount of at least one of carbon dioxide or a pH adjusting material and a therapeutic agent in the preparation of a medicament for therapeutically treating a patient, wherein said therapeutic agent is to be administered before, after, before and after, or at the same time as said carbon dioxide or pH adjusting

material; and wherein said carbon dioxide or pH adjusting material is to be delivered to a location at an interior of a nasal passage of the patient.

In another aspect, the present disclosure provides a use of about 5% to about 6% vol/vol carbon dioxide in the preparation of a medicament for increasing a therapeutic effect of a pharmaceutical agent delivered to a patient, wherein said carbon dioxide is to be delivered as a fluid flow to a posterior region of the nasal passage of the patient; and wherein said patient has been administered with a dose of the pharmaceutical agent.

In another aspect, the present disclosure provides a use of about 5% to about 6% vol/vol carbon dioxide in the preparation of a medicament for providing a therapeutic or pharmacokinetic effect, wherein said carbon dioxide is to be delivered to a nostril of the patient to lower a pH of an upper posterior region of the nasal passage by at least about 0.1 pH units.

In a further aspect, the present disclosure provides a use of a triptan and a therapeutic amount of at least one of carbon dioxide or a pH adjusting material in the preparation of a medicament for treating migraine in a patient, wherein said triptan is to be administered intranasally; and wherein said carbon dioxide or pH adjusting material is to be delivered to a location at an interior of a nasal passage of the patient , wherein the triptan is to be administered before, after, before and after, or at the same time as the carbon dioxide or pH adjusting material is delivered; wherein less than 2% of treated patients exhibit atypical triptan sensations consisting of tingling, warm/hot sensation, burning sensation, feeling

of heaviness, pressure, feeling of tightness, including tightness in the head, numbness and feeling strange.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a pH of the mucosa, before, during or

In one embodiment the method further comprises: the subject exhaling through a mouthpiece to cause closure of the oropharyngeal velum of the subject.

In one embodiment the mouthpiece is fluidly connected to a nosepiece, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a pressure in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

In one embodiment the mucosa is also innervated by the sphenopalatine ganglion.

In one embodiment the substance is delivered through a nosepiece fitted to a nostril, optionally being a fluid-tight seal with a nare of the nostril.

In one embodiment, the substance is delivered through a single nostril to the mucosa at one trigeminal nerve.

In one embodiment the substance is delivered successively through each of the nostrils to the mucosa at each of the trigeminal nerves.

In one embodiment the pressure is adjusted by delivery of at least one gas.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a concentration of NO in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance in increased.

In one embodiment the mucosa is also innervated by the sphenopalatine ganglion.

In one embodiment the substance is delivered through a nosepiece fitted to a nostril, optionally being a fluid-tight seal with a nare of the nostril.

In one embodiment the substance is delivered through a single nostril to the mucosa at one trigeminal nerve.

In one embodiment the substance is delivered successively through each of the nostrils to the mucosa at each of the trigeminal nerves.

In one embodiment the NO concentration is adjusted by delivery of at least one gas.

In one embodiment the at least one gas is delivered in a flow, optionally having a concentration of at least 5 vol% of the at least one gas.

In one embodiment the at least one gas comprises carbon dioxide.

In one embodiment adjustment of the NO concentration mediates activity at the V1 branch of the trigeminal nerve.

In one embodiment the NO concentration is decreased in the NO concentration adjustment.

In one embodiment the method further comprises: the subject exhaling through a mouthpiece to cause closure of the oropharyngeal velum of the subject.

In one embodiment the mouthpiece is fluidly connected to a nosepiece, whereby exhaled air from an exhalation breath is delivered through the nosepiece.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a pH of the mucosa before, during or after the delivery of a substance; and adjusting a pressure in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a pH of the mucosa before, during or after the delivery of a substance; and adjusting a concentration of NO in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising

mucosa innervated by a trigeminal nerve; adjusting a pressure in the nasal cavity before, during or after the delivery of the substance; and adjusting a concentration of NO in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance in increased.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a posterior region of the nasal cavity of the subject, the posterior region comprising mucosa innervated by a trigeminal nerve; adjusting a pH of the mucosa before, during or after the delivery of the substance; and adjusting a pressure in the nasal cavity before, during or after the delivery of the substance; and adjusting a concentration of NO in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a substance for treating a neurological or CNS disorder, wherein the substance is delivered to a posterior region of the nasal cavity of a subject, the posterior region comprising mucosa innervated by a trigeminal nerve; and wherein a pH of the mucosa is adjusted before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides substance for treating a neurological or CNS disorder, wherein the substance is delivered to a posterior region of the nasal cavity of a subject, the posterior region comprising mucosa innervated by a trigeminal nerve; and wherein a pressure in the nasal

cavity is adjusted before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a substance for treating a neurological or CNS disorder, wherein the substance is delivered to a posterior region of the nasal cavity of a subject, the posterior region comprising mucosa innervated by a trigeminal nerve; and wherein a concentration of NO in the nasal cavity is adjusted before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

In one embodiment the substance is a triptan. In one embodiment the substance is sumatriptan.

In another embodiment the substance is an ergot alkaloid. In one embodiment the substance is an ergotamine or an analogue or derivative thereof, such as dihydroergotamine.

The substance is for the treatment of headache, including cluster headache and migraine.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a subject; adjusting a pressure in the nasal cavity before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a subject; adjusting a concentration of NO in the nasal cavity before, during or after

the delivery of the substance, whereby a rate of uptake of the substance is increased.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a substance to a subject; adjusting a pH of the mucosa innervated by a trigeminal nerve before, during or after the delivery of the substance, whereby a rate of uptake of the substance is increased.

In one embodiment the delivery is peroral, topical, transmucosal, inhalation and/or injection, sub-cutaneous, nasal and/or oral.

The present disclosure provides a method of administering a substance to a subject, comprising: delivering a first substance that induces a migraine; and delivering a second substance according to any of the methods disclose above.

In accordance with the disclosure an embodiment is directed to a method of therapeutically treating a patient. The method can include administering, in a first step, a therapeutic agent, and delivering, in a second step, to a location at an interior of a nasal passage of the patient, a therapeutic amount of at least one of carbon dioxide or a pH adjusting material.

Another embodiment is directed to a method for increasing a therapeutic effect of a pharmaceutical agent delivered to a patient. The method can include delivering a fluid flow to a nasal passage of the patient to deliver about 5% to about 6% vol/vol carbon dioxide to an upper posterior region of the nasal

CLAIMS

1. Use of a therapeutic amount of at least one of carbon dioxide or a pH adjusting material and a therapeutic agent in the preparation of a medicament for therapeutically treating a patient, wherein said therapeutic agent is to be administered before, after, before and after, or at the same time as said carbon dioxide or pH adjusting material; and wherein said carbon dioxide or pH adjusting material is to be delivered to a location at an interior of a nasal passage of the patient .

2. The use of claim 1, wherein said therapeutic agent is to be administered before said carbon dioxide or pH adjusting material is delivered.

3. The use of claim 1, wherein said therapeutic agent is to be administered after said carbon dioxide or pH adjusting material is delivered.

4. The use of claim 1, wherein said carbon dioxide or pH adjusting material is to be delivered both before and after said therapeutic agent is administered or at the same time as said therapeutic agent is administered.

5. The use of claim 1, wherein the location includes an upper posterior region of the nasal passage.

6. The use of claim 1, wherein the therapeutic agent includes a triptan, optionally sumatriptan, optionally in the form of sumatriptan succinate, optionally to be administered as a powder aerosol.

7. The use of claim 6, wherein the therapeutic agent is to be delivered in an amount not greater than 30 mg, optionally not greater than 25 mg, optionally not greater than 20 mg, optionally daily.

8. The use of claim 6, wherein the capsules each contain from 7 to 15 mg, optionally from 10 to 12 mg, optionally approximately 11 mg, of free base of sumatriptan, and optionally each yield an average delivered dose of from 5 to 10 mg, optionally from 6 to 9 mg, optionally from 7 to 9 mg, optionally approximately 8 mg.

9. The use of claim 1, wherein a first dose of said therapeutic agent from a first capsule is to be delivered into a first nostril, and a second dose of said therapeutic agent from a second capsule is to be delivered into a second nostril.

10. The use of claim 1, wherein the therapeutic agent includes a topical steroid, optionally fluticasone, optionally in the form of fluticasone propionate, optionally to be administered as a liquid aerosol.

11. The use of claim 10, wherein the therapeutic agent is to be delivered in amount of at least 75 µg daily, at least 100 µg daily, at least 200 µg daily, at least 400 µg daily or at least 800 µg daily, optionally delivered in two doses, optionally at least 37.5 µg b.i.d., at least 50 µg b.i.d., at least 100 µg b.i.d., at least 200 µg b.i.d. or at least 400 µg b.i.d..

12. The use of claim 10, wherein said carbon dioxide or pH adjusting material is to be delivered by placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient, the mouthpiece being fluidly connected to the nosepiece; and

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece;

wherein the therapeutic agent when intranasally administered has a systemic bioavailability or pharmacokinetic (PK) profile which is equivalent to or not greater than the systemic bioavailability of 50 µg of the therapeutic agent when intranasally administered without said carbon dioxide or pH adjusting material.

13. The use of claim 1, wherein said carbon dioxide or pH adjusting material adjusts a pH in the nasal passage location by an amount ranging from about 0.01 to about 0.5 pH units.

14. The use of claim 13, wherein the amount ranges from about 0.1 to about 0.2 pH units.

15. The use of claim 1, wherein the concentration of carbon dioxide from about 1% vol/vol to about 10% vol/vol carbon dioxide.

16. The use of claim 15, wherein the concentration of carbon dioxide is from about 5% to about 6% vol/vol carbon dioxide.

17. The use of claim 1, wherein said carbon dioxide or pH adjusting material is to be delivered by placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient;

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece; and

directing the fluid flow to the location within the nasal passage.

18. The use of claim 17, said delivering further comprises adjusting a pH at the location by controlling the fluid flow.

19. The use of claim 18, wherein said controlling the fluid flow includes at least one of controlling a duration, a rate, a pressure, and a composition of the fluid flow.

20. The use of claim 19, wherein the fluid flow duration is controlled to be in a range of from about 2 to about 3 s.

21. The use of claim 20, wherein the fluid flow is controlled at a rate of at least 10 L/min, optionally at least 20 L/min, and optionally at about 30 L/min.

22. The use of claim 17, wherein said delivering further comprises:

placing the nosepiece into a second nostril of the patient;

the patient exhaling a breath into the mouthpiece to create a second fluid flow out of the nosepiece; and

directing the second fluid flow to a second location within a second nasal passage.

23. Use of about 5% to about 6% vol/vol carbon dioxide in the preparation of a medicament for increasing a therapeutic effect of a pharmaceutical agent delivered to a patient, wherein said

carbon dioxide is to be delivered as a fluid flow to a posterior region of the nasal passage of the patient; and wherein said patient has been administered with a dose of the pharmaceutical agent.

24. The use of claim 23, wherein the pH of the posterior region of the nasal passage is lowered.

25. The use of claim 23, wherein the pharmaceutical agent includes a triptan, optionally sumatriptan, optionally in the form of sumatriptan succinate.

26. The use of claim 25, wherein the pharmaceutical agent is delivered in an amount not greater than 30 mg, optionally not greater than 25 mg, optionally not greater than 20 mg, optionally daily.

27. The use of claim 25, wherein the capsules each contain from 7 to 15 mg, optionally from 10 to 12 mg, optionally approximately 11 mg, of free base of sumatriptan, and optionally each yield an average delivered dose of from 5 to 10 mg, optionally from 6 to 9 mg, optionally from 7 to 9 mg, optionally approximately 8 mg.

28. The use of claim 23, wherein a first dose of therapeutic agent is to be delivered from a first capsule into a first nostril, and a second dose of therapeutic agent is to be delivered from a second capsule into a second nostril.

29. The use of claim 23, wherein the pharmaceutical agent is for treating pain relief.

30. The use of claim 23, wherein the pharmaceutical agent includes a topical steroid, optionally fluticasone, optionally in the form of fluticasone propionate.

31. The use of claim 30, wherein the therapeutic agent is delivered in amount of at least 75 µg daily, at least 100 µg daily, at least 200 µg daily, at least 400 µg daily or at least 800 µg daily, optionally delivered in two doses, optionally at least 37.5 µg b.i.d., at least 50 µg b.i.d., at least 100 µg b.i.d., at least 200 µg b.i.d. or at least 400 µg b.i.d..

32. The use of claim 30, wherein said carbon dioxide is to be delivered by placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient, the mouthpiece being fluidly connected to the nosepiece; and

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece;

and wherein the pharmaceutical agent when intranasally administered has a systemic bioavailability or pharmacokinetic (PK) profile which is equivalent to or not greater than the systemic bioavailability or pharmacokinetic (PK) profile of 50 μg of the pharmaceutical agent when intranasally administered without said carbon dioxide.

33. The use of claim 23, wherein said carbon dioxide mediates uptake of the pharmaceutical agent.

34. The use of claim 23, wherein the pharmaceutical agent is to be administered as a powder aerosol.

35. The use of claim 23, wherein the pharmaceutical agent is to be administered as a liquid aerosol.

36. The use of claim 23, wherein the pharmaceutical agent is to be administered orally, optionally in tablet form.

37. The use of claim 23, wherein the pharmaceutical agent is to be administered intravenously.

38. The use of claim 23, wherein the pharmaceutical agent is to be administered sub-cutaneously.

39. Use of about 5% to about 6% vol/vol carbon dioxide in the preparation of a medicament for providing a therapeutic or pharmacokinetic effect, wherein said carbon dioxide is to be delivered to a nostril of the patient to lower a pH of an upper posterior region of the nasal passage by at least about 0.1 pH units.

40. The use of claim 39, wherein the medicament further comprises a therapeutic agent to be administered to the patient at least one of orally, intranasally, intravenously and sub-cutaneously.

41. The use of claim 39, wherein said carbon dioxide is to be delivered by

placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient, the mouthpiece being fluidly connected to the nosepiece; and

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece.

42. The use of claim 39, wherein no substance or pharmaceutical agent other than exhaled air is to be delivered to the nasal passage.

43. The use of claim 39, the medicament further comprises a dose of a pharmaceutical agent to be administered to the patient, and wherein said carbon dioxide mediates uptake of the pharmaceutical agent.

44. The use of claim 43, wherein the pharmaceutical agent is to be administered intranasally.

45. The use of claim 44, wherein the pharmaceutical agent is to be administered as a powder aerosol.

46. The use of claim 44, wherein the pharmaceutical agent is to be administered as a liquid aerosol.

47. The use of claim 43, wherein the pharmaceutical agent is to be administered orally, optionally in tablet form.

48. The use of claim 43, wherein the pharmaceutical agent is to be administered intravenously.

49. The use of claim 43, wherein the pharmaceutical agent is to be administered sub-cutaneously.

50. The use of claim 43, wherein the pharmaceutical agent includes a triptan, optionally sumatriptan, optionally in the form of sumatriptan succinate.

51. The use of claim 50, wherein the pharmaceutical agent is delivered in an amount not greater than 30 mg, optionally not greater than 25 mg, optionally not greater than 20 mg, optionally daily.

52. The use of claim 50, wherein the capsules each contain from 7 to 15 mg, optionally from 10 to 12 mg, optionally approximately 11 mg, of free base of sumatriptan, and optionally each yield an average delivered dose of from 5 to 10 mg, optionally from 6 to 9 mg, optionally from 7 to 9 mg, optionally approximately 8 mg.

53. The use of claim 50, wherein the pharmaceutical agent is delivered in an amount of at least 50 mg, 100 mg, 150 mg or 200 mg, optionally not greater than 200 mg, 150 mg or 100 mg.

54. The use of claim 43, wherein a first dose of pharmaceutical agent from a first capsule is to be delivered into a first nostril, and a second dose of pharmaceutical agent from a second capsule is to be delivered into a second nostril.

55. The use of claim 43, wherein the pharmaceutical agent is for treating pain relief.

56. The use of claim 43, wherein the pharmaceutical agent is a topical steroid, optionally fluticasone, optionally in the form of fluticasone propionate.

57. The use of claim 56, wherein the therapeutic agent is delivered in amount of at least 75 µg daily, at least 100 µg daily, at least 200 µg daily, at least 400 µg daily or at least 800 µg daily, optionally delivered in two doses, optionally at least 37.5 µg b.i.d., at least 50 µg b.i.d., at least 100 µg b.i.d., at least 200 µg b.i.d. or at least 400 µg b.i.d..

58. The use of claim 56, wherein said carbon dioxide is delivered by

placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient, the mouthpiece being fluidly connected to the nosepiece; and

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece;

wherein the steroid when intranasally administered has a systemic bioavailability or pharmacokinetic (PK) profile which is equivalent to or not

greater than the systemic bioavailability or pharmacokinetic (PK) profile of 50 µg of the steroid when intranasally administered without said carbon dioxide.

59. The use of claim 43, wherein the therapeutic or pharmacokinetic effect treats at least one of pain, headache, migraine and allergic rhinitis.

60. The use of claim 43, wherein the patient has a substantially closed soft palate during the delivery of said carbon dioxide.

61. Use of a triptan and a therapeutic amount of at least one of carbon dioxide or a pH adjusting material in the preparation of a medicament for treating migraine in a patient, wherein said triptan is to be administered intranasally; and wherein said carbon dioxide or pH adjusting material is to be delivered to a location at an interior of a nasal passage of the patient , wherein the triptan is to be administered before, after, before and after, or at the same time as the carbon dioxide or pH adjusting material is delivered;

wherein less than 2% of treated patients exhibit atypical triptan sensations consisting of tingling, warm/hot sensation, burning sensation, feeling of heaviness, pressure, feeling of tightness, including tightness in the head, numbness and feeling strange.

62. The use of claim 61, wherein the triptan is to be administered before the carbon dioxide or pH adjusting material is delivered.

63. The use of claim 61, wherein the triptan is to be administered after the carbon dioxide or pH adjusting material is delivered.

64. The use of claim 61, wherein the carbon dioxide or the pH adjusting material is to be delivered both before and after the triptan is administered or at the same time as the triptan is administered.

65. The use of claim 61, wherein the location includes an upper posterior region of the nasal passage.

66. The use of claim 61, wherein the triptan includes sumatriptan, optionally in the form of sumatriptan succinate.

67. The use of claim 66, wherein less than 30 mg of sumatriptan is delivered to the nasal passage, optionally less than 25 mg, optionally less than 20 mg, optionally daily.

68. The use of claim 66, wherein the capsules each contain from 7 to 15 mg, optionally from 10 to 12 mg, optionally approximately 11 mg, of free base of sumatriptan, and optionally each yield an average delivered

dose of from 5 to 10 mg, optionally from 6 to 9 mg, optionally from 7 to 9 mg, optionally approximately 8 mg.

69. The use of claim 61, wherein a first dose of the triptan is to be delivered from a first capsule into a first nostril, and a second dose of the triptan is to be delivered from a second capsule into a second nostril.

70. The use of claim 61, wherein the carbon dioxide or the pH adjusting material adjusts a pH in the nasal passage location by an amount ranging from about 0.01 to about 0.5 pH units.

71. The use of claim 70, wherein the amount ranges from about 0.1 to about 0.2 pH units.

72. The use of claim 61, wherein the the concentration of carbon dioxide from about 1% vol/vol to about 10% vol/vol carbon dioxide.

73. The use of claim 72, wherein the concentration of carbon dioxide is from about 5% to about 6% vol/vol carbon dioxide.

74. The use of claim 61, wherein the said carbon dioxide or pH adjusting material is to be delivered by placing a mouthpiece into a mouth of the patient and a nosepiece into a nostril of the patient;

the patient exhaling a breath into the mouthpiece to create a fluid flow out of the nosepiece; and

directing the fluid flow to the location within the nasal passage.

75. The use of claim 74, wherein said delivering further comprises adjusting a pH at the location by controlling the fluid flow.

76. The use of claim 75, wherein said controlling the fluid flow includes at least one of controlling a duration, a rate, a pressure, and a composition of the fluid flow.

77. The use of claim 76, wherein the fluid flow duration is controlled to be in a range of from about 2 to about 3 s.

78. The use of claim 77, wherein the fluid flow is controlled at a rate of at least 10 L/min, optionally at least 20 L/min, and optionally at about 30 L/min.

79. The use of claim 74, wherein said delivering further comprises:

placing the nosepiece into a second nostril of the patient;

the patient exhaling a breath into the mouthpiece to create a second fluid flow out of the nosepiece; and

directing the second fluid flow to a second location within a second nasal passage.

80. The use of claim 61, wherein the pain relief achieved at 10 minutes following administration is at least 12%, optionally at least 13%, and/or the pain relief achieved at 15 minutes following administration is at least 22%, optionally at least 25%, and/or the pain relief achieved at 30 minutes following administration is at least 45%, optionally at least 50%, and/or the pain relief achieved at 60 minutes following administration is at least 65%, optionally at least 70%.