

Claims:

1. ~~A method of reducing or preventing pain in a subject in need thereof, the method comprising administering to the subject a subcutaneous fixed dose of~~ Use of a binding molecule in the manufacture of a medicament for reducing or preventing pain in a subject in need thereof, wherein the a subcutaneous fixed dose of the binding molecule is to be administered to the subject, wherein the binding molecule comprises an NGF antagonist domain and a TNF α antagonist domain, wherein the NGF antagonist domain is an anti-NGF antibody or an antigen-binding fragment thereof, and wherein the TNF α antagonist domain comprises a soluble TNF α binding fragment of TNFR, ~~and wherein the method reduces or prevents pain in the subject.~~
2. A binding molecule for use in a method of reducing or preventing pain in a subject in need thereof, wherein a subcutaneous fixed dose of a binding molecule is to be administered to the subject, wherein the binding molecule comprises an NGF antagonist domain and a TNF α antagonist domain, wherein the NGF antagonist domain is an anti-NGF antibody or an antigen-binding fragment thereof, wherein the TNF α antagonist domain comprises a soluble TNF α binding fragment of TNFR.
32. ~~The use method of claim 1 or the binding molecule for use of claim 2, wherein the subcutaneous fixed dose of the binding molecule is:~~
 - ~~(a) about 5 to 200 mg;~~
3. ~~The method of any preceding claim, wherein the subcutaneous fixed dose of the binding molecule is~~ (b) about 7.5 to 150 mg.
4. ~~The method of any preceding claim, wherein the subcutaneous fixed dose of the binding molecule is~~ (c) about 7.5 mg, about 25 mg, about 75 mg or about 150 mg; and/or
5. ~~The method of any preceding claim, wherein the subcutaneous fixed dose is~~ (d) equivalent to an intravenous fixed dose of 30 mg of the binding molecule.
64. ~~The use method of claim 1 or 3, or the binding molecule for use of claim 2 or 3~~ any preceding claim, wherein the fixed dose is to be administered:
 - (a) at least once every two weeks; and/or
7. ~~The method of any preceding claim, wherein the fixed dose is administered~~ (b) for at least 12 weeks.
85. ~~The use method of any one of claims 1, 3 and 4, or the binding molecule for use of any one of claims 2-4~~ preceding claim, wherein:
 - (a) the pain comprises chronic pain;

- ~~9. The method of any preceding claim, wherein (b) the pain comprises osteoarthritic pain;~~
- ~~10. The method of any preceding claim, wherein (c) the pain comprises osteoarthritic pain of the knee;~~
- ~~11. The method of any preceding claim, wherein (d) the subject has suffered the pain for 3 months or longer prior to administration with the binding molecule;~~
- ~~12. The method of any preceding claim, wherein (e) the pain is associated with joint inflammation;~~
- ~~13. The method of any preceding claim, wherein (f) the subject has osteoarthritis; optionally wherein the subject has at least Grade 2 osteoarthritis of the knee joint on the Kellgren-Lawrence (KL) grading scale of 0 to 4 as per central reader evaluation; and/or~~
- ~~14. The method of claim 13, wherein (g) the subject has unilateral osteoarthritis of the knee;~~
- ~~15. The method of claim 13 or 14, optionally wherein the subject has at least Grade 2 osteoarthritis of the knee joint on the Kellgren-Lawrence (KL) grading scale of 0 to 4 as per central reader evaluation.~~
- ~~166. The use method of any one of claims 1 and 3-5, or the binding molecule for use of any one of claims 2-5~~
~~preceding claim, wherein:~~
- ~~(a) comprising the following steps prior to administration of the binding molecule to the subject:~~
- ~~(i) administering to the subject a NSAID, strong opioid, weak opioid, COX-2 inhibitor, acetaminophen or a combination thereof is to be administered to the subject, and~~
- ~~(ii) determining that (i) that the NSAID, strong opioid, weak opioid, COX-2 inhibitor, acetaminophen or a combination thereof does not reduce or prevent pain in the subject, and/or (ii) determining that the subject is intolerant to the NSAID, strong opioid, weak opioid, COX-2 inhibitor, acetaminophen or a combination thereof;~~
- ~~17. The method of claim 16, optionally wherein the NSAID, strong opioid, weak opioid, COX-2 inhibitor, acetaminophen or a combination thereof is to be administered for at least 2 weeks; or~~
- ~~18. The method of claim 16, wherein the NSAID, strong opioid, weak opioid, COX-2 inhibitor, acetaminophen or a combination thereof has been administered to the subject for at least 2 weeks prior to administration with the binding molecule; and/or~~
- ~~19. The method of any preceding claim, wherein (b) the subject is intolerant to NSAIDs, strong opioids, weak opioids, COX-2 inhibitors, acetaminophen or a combination thereof.~~

~~207.~~ The ~~use method~~ of any one of claims 1 and 3-6, or the binding molecule for use of any one of claims 2-6~~preceding claim~~, wherein:

~~(a) the method comprises testing the subject is to be tested for SARS-CoV2 infection prior to administration with the fixed dose of the binding molecule;~~

~~21. The method of claim 20, optionally wherein testing the subject is to be tested for SARS-CoV2 infection wherein comprises testing the subject is to be tested for SARS-CoV2 genetic material prior to administration with the fixed dose of the binding molecule; and/or~~

~~22. The method of any preceding claim, wherein (b) the subject is not infected with SARS-CoV2 at baseline.~~

~~238.~~ The ~~use method~~ of any one of claims 1 and 3-7, or the binding molecule for use of any one of claims 2-7~~preceding claim~~, wherein:

~~(a) the subject has a mean Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score of at least 5 in a joint as measured using the pain subscale of the WOMAC index at baseline; and/or~~

~~24. The method of any preceding claim, wherein (b) the subject has a mean pain intensity score of at least 5 in a joint as measured on a pain numerical rating scale (NRS) at baseline.~~

~~259.~~ The ~~use method~~ of any one of claims 1 and 3-8, or the binding molecule for use of any one of claims 2-8~~preceding claim~~, wherein:

~~(a) the method reduces the subject's weekly average of daily NRS pain score is to be reduced from baseline;~~

~~26. The method of any preceding claim, wherein (b) the fixed dose is to be administered every 2 weeks for 12 weeks, and wherein the method reduces the subject's weekly average of daily NRS pain score is to be reduced from baseline by at least week 12;~~

~~27. The method of any preceding claim, wherein (c) the method reduces the subject's weekly average of daily NRS pain score is to be reduced from baseline by at least 30%; and/or~~

~~28. The method of any preceding claim, wherein (d) the method reduces the subject's weekly average of daily NRS pain score is to be reduced from baseline by at least 50%.~~

~~2910.~~ The ~~use method~~ of any one of claims 1 and 3-9, or the binding molecule for use of any one of claims 2-9~~preceding claim~~, wherein:

~~(a) the method reduces the subject's WOMAC pain subscale score is to be reduced from baseline;~~

~~30. The method of any preceding claim, wherein (b) the fixed dose is to be administered every 2 weeks for 12 weeks, and wherein the method reduces the subject's WOMAC pain subscale score is to be reduced from baseline by at least week 12;~~

~~31. The method of any preceding claim, wherein (c) the method reduces the subject's WOMAC pain subscale score is to be reduced from baseline by at least 30%;~~

~~32. The method of any preceding claim, wherein (d) the method reduces the subject's WOMAC pain subscale score is to be reduced from baseline by at least 50%;~~

~~33. The method of any preceding claim, wherein (e) the method reduces the subject's WOMAC physical subscale score is to be reduced from baseline by at least 30%; and/or~~

~~34. The method of any preceding claim, wherein (f) the method reduces the subject's WOMAC physical subscale score is to be reduced from baseline by at least 50%.~~

~~3511. The use method of any one of claims 1 and 3-10, or the binding molecule for use of any one of claims 2-10~~preceding claim, wherein:

~~(a) the method improves the Patient Global Assessment (PGA) of osteoarthritis is to be improved from baseline;~~

~~36. The method of any preceding claim, wherein (b) the fixed dose is to be administered every 2 weeks for 12 weeks, and wherein method improves the PGA of osteoarthritis is to be improved from baseline by at least week 12; and/or~~

~~37. The method of any preceding claim, wherein (c) the method improves the PGA of osteoarthritis is to be improved by at least 2 points.~~

~~3812. The use method of any one of claims 1 and 3-11, or the binding molecule for use of any one of claims 2-11~~preceding claim, wherein pain reduction is observed following a single dose administration of the binding molecule in the subject.

~~3913. The use method of any one of claims 1 and 3-12, or the binding molecule for use of any one of claims 2-12~~preceding claim, wherein the subject is to be administered method comprises administering:

~~(a) an NSAID to the subject;~~

~~40. The method of any preceding claim, wherein the method comprises administering (b) an opioid to the subject;~~

~~41. The method of any preceding claim, wherein the method comprises administering (c) acetaminophen to the subject; and/or~~

~~42. The method of any preceding claim, wherein the method comprises administering (d) a COX-2 inhibitor to the subject.~~

~~4314.~~ The ~~use method~~ of any one of claims 1 and 3-13, or the binding molecule for use of any one of claims 2-13 ~~preceding claim~~, wherein the anti-NGF antibody or fragment thereof:

~~(a)~~ can inhibit NGF binding to TrkA, p75NRT, or both TrkA and P75NRT;

~~44. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof~~
~~(b)~~ preferentially blocks NGF binding to TrkA over NGF binding to p75NRT; and/or

~~45. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof~~
~~(c)~~ binds human NGF with an affinity of about 0.25-0.44 nM.

~~4615.~~ The ~~use method~~ of any one of claims 1 and 3-14, or the binding molecule for use of any one of claims 2-14 ~~preceding claim~~, wherein the anti-NGF antibody or fragment thereof comprises:

~~(a)~~ an antibody VH domain comprising a set of CDRs HCDR1, HCDR2, HCDR3 and an antibody VL domain comprising a set of CDRs LCDR1, LCDR2 and LCDR3, wherein the HCDR1 has the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 4 with up to two amino acid substitutions, the HCDR2 has the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 5 with up to two amino acid substitutions, the HCDR3 has the amino acid sequence of SEQ ID NO: 6 or SEQ ID NO: 6 with up to two amino acid substitutions, SSRIYDFNSALISYYDMDV (SEQ ID NO: 11), or SSRIYDMISLQPYDMDV (SEQ ID NO:12), the LCDR1 has the amino acid sequence of SEQ ID NO: 8 or SEQ ID NO: 8 with up to two amino acid substitutions, the LCDR2 has the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 9 with up to two amino acid substitutions, and the LCDR3 has the amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 10 with up to two amino acid substitutions;

~~47. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof~~
~~comprises~~ ~~(b)~~ an antibody VH domain comprising a set of CDRs HCDR1, HCDR2, HCDR3 and an antibody VL domain comprising a set of CDRs LCDR1, LCDR2 and LCDR3,

wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 4,

the HCDR2 comprises the amino acid sequence of SEQ ID NO: 5,

the HCDR3 comprises the amino acid sequence of SEQ ID NO: 6, SSRIYDFNSALISYYDMDV (SEQ ID NO: 11), or SSRIYDMISLQPYDMDV (SEQ ID NO:12),

the LCDR1 comprises the amino acid sequence of SEQ ID NO: 8,

the LCDR2 comprises the amino acid sequence of SEQ ID NO: 9; and

the LCDR3 comprises the amino acid sequence of SEQ ID NO: 10;

~~48. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof comprises (c) a VH having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 3 or 94; and/or~~

~~49. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof comprises (d) a VL having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7 or 95.~~

~~5016. The use method of any one of claims 1 and 3-15, or the binding molecule for use of any one of claims 2-15preceding claim, wherein the anti-NGF antibody or fragment thereof is:~~

~~(a) a full H₂L₂ antibody, a Fab, fragment, an Fab' fragment, an F(ab)₂ fragment or a single chain Fv (scFv) fragment; and/or~~

~~51. The method of any preceding claim, wherein the anti-NGF antibody or fragment thereof is (b) humanized, chimeric, primatized, or fully human.~~

~~5217. The use method of any one of claims 1 and 3-16, or the binding molecule for use of any one of claims 2-16preceding claim, wherein the anti-NGF scFv fragment comprises, from N-terminus to C-terminus:~~

~~(a) a VH comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 3, a 15-amino acid linker sequence (GGGGS)₃ (SEQ ID NO: 15), and a VL comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7; and/or~~

~~53. The method of any preceding claim, wherein the anti-NGF scFv fragment comprises, from N-terminus to C-terminus, (b) a VH comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 94, a 20-amino acid linker sequence (GGGGS)₄ (SEQ ID NO:19), and a VL comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 95.~~

~~5418. The use method of any one of claims 1 and 3-17, or the binding molecule for use of any one of claims 2-17preceding claim, wherein:~~

~~(a) the TNFR is TNFR-2;~~

~~55. The method of any preceding claim, wherein optionally wherein the TNFR-2 fragment is fused to an immunoglobulin Fc domain; optionally wherein~~

~~56. The method of any preceding claim, wherein the immunoglobulin Fc domain is a human IgG1 Fc domain;~~ and/or

~~57. The method of any preceding claim, wherein~~ (b) the TNF α antagonist domain comprises an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence set forth in SEQ ID NO: 13, or a functional fragment thereof.

~~58~~19. The method-use of any one of claims 1 and 3-18, or the binding molecule for use of any one of claims 2-18~~preceding claim, wherein:~~

(a) the binding molecule comprises a fusion protein that comprises the NGF antagonist domain fused to the TNF α antagonist domain through a linker; optionally wherein

~~59. The method of any preceding claim, wherein the binding molecule comprises a homodimer of the fusion protein;~~

~~60. The method of any preceding claim, wherein~~ (b) the binding molecule comprises a homodimer of a fusion polypeptide comprising, from N-terminus to C-terminus, a TNF α -binding fragment of TNFR-2 comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to a sequence corresponding to amino acids 1-235 of SEQ ID NO: 13, a human IgG1Fc domain, a 10 amino-acid linker sequence (GGGGS)₂ (SEQ ID NO: 98), a VH comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO 3 or 94, a 15-amino acid linker sequence (GGGGS)₃ (SEQ ID NO: 15), and a VL comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 7 or 95;

~~61. The method of any preceding claim, wherein~~ (c) the binding molecule comprises a homodimer of a fusion polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 97%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 14;

~~62. The method of any preceding claim, wherein~~ (d) the binding molecule comprises a homodimer of a fusion polypeptide comprising, from N-terminus to C-terminus, a TNF α -binding 75kD fragment of TNFR-2 comprising the amino acid sequence of SEQ ID NO: 13, a 10-amino-acid linker sequence (GGGGS)₂ (SEQ ID NO: 98), a VH comprising the amino acid sequence of SEQ ID NO: 94, a 20-amino acid linker sequence (GGGGS)₄ (SEQ ID NO: 19), and a VL comprising the amino acid sequence of SEQ ID NO: 95;

~~63. The method of any preceding claim, wherein~~ (e) the glycine residue at the amino acid position corresponding to position 102, 103, or 104 of SEQ ID NO: 7 is modified to a cysteine residue, and wherein the glycine residue at the amino acid position corresponding to position 44 of SEQ ID NO: 3 is modified to a cysteine residue;

- ~~64. The method of any preceding claim, wherein (f) the binding molecule comprises a homodimer of a fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 17; and/or~~
- ~~65. The method of any preceding claim, wherein (g) the binding molecule comprises a homodimer of a fusion polypeptide comprising an amino acid sequence that is at least 80%, 85%, 90%, 95% or 99% identical to the amino acid sequence of SEQ ID NO: 17.~~
- ~~66. A binding molecule for use in a method of reducing or preventing pain in a subject in need thereof, the method comprising administering to the subject a subcutaneous fixed dose of a binding molecule, wherein the binding molecule comprises an NGF antagonist domain and a TNF α antagonist domain, wherein the NGF antagonist domain is an anti-NGF antibody or an antigen-binding fragment thereof, wherein the TNF α antagonist domain comprises a soluble TNF α binding fragment of TNFR, and wherein the method reduces or prevents pain in the subject.~~
- ~~67. A binding molecule for use in a method of any of claims 1-65.~~