

CLAIMS

1. A method of decreasing the formation of new heterotopic ossification lesions in a human subject with FOP, the method comprising administering to the human subject a therapeutically effective amount of an Activin A antagonist, thereby decreasing the formation of new heterotopic ossification lesions in the human subject.

2. The method of claim 1, wherein the formation of new heterotopic ossification lesions is prevented in the human subject.

3. A method of preventing formation of new heterotopic ossification lesions in a human subject with FOP, the method comprising administering to the human subject a therapeutically effective amount of an Activin A antagonist, thereby preventing the formation of new heterotopic ossification lesions in the human subject.

4. The method of any one of the previous claims, wherein the human subject exhibits a decrease in number of new heterotopic ossification lesions of at least 5%, at least 10%, at least 20%, at least about 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 5%-90%, at least 10%-90%, at least 20%-90%, at least 30%-90%, at least 40%-90%, at least 50%-90%, at least 60%-90%, at least 70%-90%, at least 80%-90%, at least 5%-80%, at least 5%-70%, at least 5%-60%, at least 5%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

5. The method of any one of the previous claims, wherein the human subject exhibits a decrease in new heterotopic ossification lesion volume by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 5%-50%, at least 10%-50%, at least 20%-50%, at least 30%-50%, at least 40%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

6. The method of any one of the previous claims, wherein the human subject exhibits a decrease in a rate of new heterotopic ossification lesion growth and mineralization

of at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 5%-50%, at least 10%-50%, at least 20%-50%, at least 30%-50%, at least 40%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

7. The method of any one of the previous claims, wherein the human subject exhibits a decrease in new heterotopic ossification lesion intensity of at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50% at least 5%-50%, at least 10%-50%, at least 20%-50%, at least 30%-50%, at least 40%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

8. The method of any one of the previous claims, wherein the human subject exhibits a decrease in total lesion activity (TLA) of the heterotopic ossification lesions of at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 5%-80%, at least 10%-80%, at least 20%-80%, at least 30%-80%, at least 40%-80%, at least 50%-80%, at least 60%-80%, at least 70%-80%, at least 5%-70%, at least 5%-60%, at least 5%-50%, at least 5%-40%, at least 5%-30%, at least 5%-20%, or at least 5%-10%, relative to a control.

9. The method of any one of the previous claims, wherein the human subject exhibits a decrease in daily average pain-NRS of about 0.2-fold, 0.5-fold, 1-fold, 1.5-fold, 2-fold, 3-fold, 0.2 to 3-fold, 0.5 to 3-fold, 1 to 3-fold, 1.5 to 3-fold, 2 to 3-fold, 2.5 to 3-fold, 0.2 to 2.5-fold, 0.2 to 2-fold, 0.2 to 1.5-fold, 0.2 to 1-fold, or 0.2 to 0.5-fold, relative to a control.

10. The method of any one of claims 4-9, wherein the control is an average measurement or value gathered from a population of human subjects having FOP who have not been administered the Activin A antagonist.

11. The method of any one of the previous claims, wherein the therapeutically effective amount of an Activin A antagonist reduces the occurrence of painful flare-ups in the human subject, relative to a control.

12. The method of any one of the previous claims, wherein the new heterotopic ossification lesions are analyzed by a Positron emission tomography (PET) scan, a computed tomography (CT) scan, or a combination thereof.

13. The method of claim 12, wherein the PET scan analysis is performed by administration of radiolabeled ^{18}F sodium fluoride (^{18}F -NaF) to the human subject.

14. The method of any one of the previous claims, wherein the therapeutically effective amount of an Activin A antagonist is administered to the human subject for at least 8 weeks.

15. The method of any one of the previous claims, further comprising selecting a subject having FOP who would benefit from decreasing formation of new heterotopic ossification lesions.

16. The method of claim 15, wherein the subject who would benefit from decreasing formation of new heterotopic ossification lesions is about to undergo surgery.

17. The method of any one of the previous claims, wherein the human subject is about to undergo therapeutic treatment for FOP.

18. The method of any one of the previous claims, wherein the Activin A antagonist does not decrease the number, volume, or size of any pre-existing lesions in the human subject.

19. The method of any one of the previous claims, wherein the Activin A antagonist is a protein or a small molecule.

20. The method of any one of claims 1-18, wherein the Activin A antagonist is an anti-Activin A antibody, or antigen-binding fragment thereof.

21. The method of claim 20, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, is a chimeric, veneered, humanized or human antibody, or antigen-binding fragment thereof.

22. The method of claim 20 or claim 21, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, is a human kappa IgG1 antibody.

23. The method of claim 20 or claim 21, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises the following six CDR sequences:

- (a) an HCDR1 having at least about 80% identity to the sequence GGSFSSHF;
- (b) an HCDR2 having at least about 80% identity to the sequence ILYTGGT;
- (c) an HCDR3 having at least about 80% identity to the sequence
ARARSGITFTGIIVPGSFDI;
- (d) an LCDR1 having at least about 80% identity to the sequence QSVSSSY;
- (e) an LCDR2 having at least about 80% identity to the sequence GAS; and
- (f) an LCDR3 having at least about 80% identity to the sequence QQYGSSPWT.

24. The method of claim 23, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises the following six CDR sequences:

- (a) an HCDR1 having the sequence GGSFSSHF;
- (b) an HCDR2 having the sequence ILYTGGT;
- (c) an HCDR3 having the sequence ARARSGITFTGIIVPGSFDI;
- (d) an LCDR1 having the sequence QSVSSSY;
- (e) an LCDR2 having the sequence GAS; and
- (f) an LCDR3 having the sequence QQYGSSPWT.

25. The method of claim 24, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region having at least 90% identity with SEQ ID NO:1 and a light chain variable region having at least 90% identity with SEQ ID NO:5.

26. The method of claim 25, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region having at least 95%

identity with SEQ ID NO:1 and a light chain variable region having at least 95% identity with SEQ ID NO:5.

27. The method of claim 26, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region comprising SEQ ID NO:1 and a light chain variable region comprising SEQ ID NO:5.

28. The method of claim 27, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises a heavy chain comprising SEQ ID NO:25 and a light chain comprising SEQ ID NO:26.

29. The method of claim 20 or claim 21, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region having at least 90% identity with SEQ ID NO:1 and a light chain variable region having at least 90% identity with SEQ ID NO:5.

30. The method of claim 20 or claim 21, wherein the anti-Activin A antibody, or antigen-binding fragment thereof, competes for binding with an antibody comprising the following six CDR sequences:

- (a) an HCDR1 having the sequence GGSFSSHf;
- (b) an HCDR2 having the sequence ILYTGgT;
- (c) an HCDR3 having the sequence ARARSGITFTGIIVPGSFDI;
- (d) an LCDR1 having the sequence QSVSSSY;
- (e) an LCDR2 having the sequence GAS; and
- (f) an LCDR3 having the sequence QQYGSSPWT.

31. The method of any one of the previous claims, wherein the Activin A antagonist is administered in combination with a second therapy.