

CLAIMS

1. Use of a therapeutically effective amount of nusinersen or a nusinersen salt in the manufacture of a medicament for treating spinal muscular atrophy (SMA) in a human subject in need thereof, wherein the human subject has been previously determined to have, in a biological sample obtained from the human subject, a neurofilament level prior to initiation of the treatment that is higher than a control.
2. Use of a therapeutically effective amount of nusinersen or a nusinersen salt in the manufacture of a medicament for treating SMA in a human subject in need thereof, wherein the human subject has been previously determined to have, in a biological sample obtained from the human subject, a neurofilament level prior to initiation of the treatment.
3. The use of claim 1 or claim 2, wherein the neurofilament level in the biological sample is above 400 pg/mL.
4. Use of an SMA therapy in the manufacture of a medicament for treating SMA in a human subject in need thereof, wherein a neurofilament level is measured in a first biological sample obtained from the human subject before initiation of the SMA therapy, and wherein a neurofilament level is measured in a second biological sample obtained from the human subject after initiation of the SMA therapy.
5. The use of claim 4, wherein the neurofilament level measured in the second biological sample is lower than the neurofilament level measured in the first biological sample.
6. The use of claim 5, wherein the neurofilament level measured in the second biological sample is between 10% to 95% of the neurofilament level measured in the first biological sample.
7. The use of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject 40-90 days after initiation of the SMA therapy.

8. The use of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject 50-80 days after initiation of the SMA therapy.
9. The use of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject 60-70 days after initiation of the SMA therapy.
10. The use of any one of claims 4 to 6, wherein the second biological sample is obtained from the human subject about 64 days after initiation of the SMA therapy.
11. The use of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 50% compared to the neurofilament level measured in the first biological sample.
12. The use of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 60% compared to the neurofilament level measured in the first biological sample.
13. The use of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by at least 70% compared to the neurofilament level measured in the first biological sample.
14. The use of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by less than 50% compared to the neurofilament level measured in the first biological sample.
15. The use of any one of claims 7 to 10, wherein the neurofilament level measured in the second biological sample is reduced by less than 40% compared to the neurofilament level measured in the first biological sample.

16. The use of any one of claims 7 to 15, wherein the dose of the SMA therapy is changed for a subsequent administration to the human subject based upon the percent reduction in neurofilament level measured in the second biological sample as compared to the neurofilament level measured in the first biological sample.

17. The use of claim 4, wherein the neurofilament level measured in the second biological sample is higher than the neurofilament level measured in the first biological sample.

18. The use of any one of claims 4 to 17, wherein administration of the SMA therapy is continued.

19. The use of any one of claims 4 to 18, wherein the SMA therapy is nusinersen or a nusinersen salt.

20. The use of claim 17, wherein administration of the SMA therapy is discontinued.

21. The use of claim 20, wherein a different SMA therapy is to be administered to the human subject after discontinuing the SMA therapy.

22. The use of claim 21, wherein the different SMA therapy is nusinersen or a nusinersen salt.

23. The use of any one of claims 4 to 22, wherein the neurofilament level in the first biological sample is above 300 pg/mL.

24. The use of any one of claims 4 to 22, wherein the neurofilament level in the first biological sample is above 5,000 pg/mL.

25. Use of an SMA therapy in the manufacture of a medicament for treating spinal muscular atrophy (SMA) in a human subject in need thereof, wherein a neurofilament level is measured in a first biological sample obtained from the human subject before administration of a candidate

amount of the SMA therapy, and wherein a neurofilament level is measured in a second biological sample obtained from the human subject after administration of the candidate amount of the SMA therapy, wherein the neurofilament level in the second biological sample is lower than the neurofilament level in the first biological sample, thereby indicating that the candidate amount of the SMA therapy is a therapeutically effective amount.

26. A method of predicting the prognosis of spinal muscular atrophy (SMA), comprising:

measuring a neurofilament level in a biological sample obtained from a human subject having mutations in both copies of the SMN1 gene that lead to functional SMN protein deficiency; and

comparing the neurofilament level measured in the biological sample to a control, wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the subject will develop.

27. The method of claim 26, wherein the biological sample is obtained from the human subject before initiation of treatment with nusinersen or a nusinersen salt, and wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the human subject will develop in the absence of treatment.

28. The method of claim 26, wherein the biological sample is obtained from the human subject after initiation of treatment with nusinersen or a nusinersen salt, and wherein the neurofilament level measured in the biological sample, as compared to the control, is predictive of the severity or type of SMA that the subject will develop while receiving the treatment.

29. The method of claim 28, wherein the biological sample is obtained from the human subject at least two weeks after initiation of the treatment.

30. The method of claim 28, wherein the biological sample is obtained from the human subject at least two months after initiation of the treatment.

31. A method of predicting the prognosis of spinal muscular atrophy (SMA), comprising:
- measuring, before initiation of treatment, a neurofilament level in a first biological sample obtained from a human subject having mutations in both copies of the SMN1 gene that lead to functional SMN protein deficiency;
 - measuring a neurofilament level in a second biological sample obtained from the human subject after initiation of treatment with nusinersen or a nusinersen salt; and
 - comparing the neurofilament level measured in the second biological sample to the neurofilament level measured in the first biological sample,
- wherein the neurofilament level measured in the second biological sample, as compared to the neurofilament level measured in the first biological sample, is predictive of the severity or type of SMA that the subject will develop.
32. The method of claim 31, wherein the second biological sample is obtained from the human subject 40-90 days after initiation of the treatment.
33. The method of claim 31, wherein the second biological sample is obtained from the human subject 50-80 days after initiation of the treatment.
34. The method of claim 31, wherein the second biological sample is obtained from the human subject 60-70 days after initiation of the treatment.
35. The method of claim 31, wherein the second biological sample is obtained from the human subject about 64 days after initiation of the treatment.
36. The method of any one of claims 31 to 35, wherein the neurofilament level measured in the second biological sample is reduced by at least 50% compared to the neurofilament level measured in the first biological sample.

37. The method of any one of claims 31 to 35, wherein the neurofilament level measured in the second biological sample is reduced by at least 60% compared to the neurofilament level measured in the first biological sample.

38. The method of any one of claims 31 to 35, wherein the neurofilament level measured in the second biological sample is reduced by at least 70% compared to the neurofilament level measured in the first biological sample.

39. The method of any one of claims 31 to 35, wherein the neurofilament level measured in the second biological sample is reduced by less than 50% compared to the neurofilament level measured in the first biological sample.

40. The method of any one of claims 31 to 35, wherein the neurofilament level measured in the second biological sample is reduced by less than 40% compared to the neurofilament level measured in the first biological sample.

41. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 40, wherein the control is a pre-established neurofilament cut-off value.

42. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 40, wherein the control is the neurofilament level in a biological sample or biological samples obtained from one or more human subjects that do not have SMA.

43. A method for measuring a neurofilament level, comprising:
 providing a biological sample obtained from a human subject having mutations in both copies of the SMN1 gene that lead to functional SMN protein deficiency; and
 measuring a neurofilament level in the biological sample.

44. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 43, wherein the neurofilament is a

neurofilament heavy chain.

45. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 44, wherein the neurofilament is a phosphorylated neurofilament heavy chain.

46. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 43, wherein the neurofilament is a neurofilament medium/intermediate chain.

47. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 43, wherein the neurofilament is a neurofilament light chain.

48. The use of any one of claims 1 to 25 or the method of any one of claims 26 to 47, wherein the biological sample is blood, serum, plasma, or cerebrospinal fluid.

49. A therapeutically effective amount of nusinersen or a nusinersen salt, for use in treating SMA in a human subject in need thereof, wherein the human subject has been previously determined to have, in a biological sample obtained from the human subject, a neurofilament level prior to initiation of the treatment that is higher than a control.

50. A therapeutically effective amount of nusinersen or a nusinersen salt, for use in treating SMA in a human subject in need thereof, wherein the human subject has been previously determined to have, in a biological sample obtained from the human subject, a neurofilament level prior to initiation of the treatment.

51. An SMA therapy for use in treating SMA in a human subject in need thereof, wherein
a neurofilament level in a first biological sample obtained from the human subject
before initiation of the SMA therapy had been measured;
and
a neurofilament level in a second biological sample obtained from the human subject
after initiation of the SMA therapy is measured.

52. An SMA therapy for use in treating SMA in a human subject in need thereof, wherein:

a neurofilament level in a first biological sample obtained from the human subject has been measured, before administration of a candidate amount of the SMA therapy;

a neurofilament level in a second biological sample obtained from the human subject has been measured after administration of the candidate amount of the SMA therapy, wherein the neurofilament level in the second biological sample is lower than the neurofilament level in the first biological sample, thereby indicating that the candidate amount of the SMA therapy is a therapeutically effective amount; and wherein after having measured the lowered neurofilament level in the second biological sample; the therapeutically effective amount of the SMA therapy is to be administered to the human subject.