CLAIMS

What is claimed is:

1. A method of treating relapsing multiple sclerosis (RMS) in a subject in need thereof, comprising administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

2. A method of reducing Annualized Relapse Rate (ARR) and reducing the risk of experiencing cCDP12 in a subject with RMS, comprising administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or 2, comprising evaluating the onset of composite 12-week confirmed disability progression (cCDP12), wherein onset of cCDP12 comprises at least one of:

(a) an increase from baseline in EDSS score of at least 1.0 point in a subject with a baseline EDSS score of less than or equal to 5.5 points; or an increase from baseline in EDSS score of at least 0.5 point in a subject with a baseline EDSS score of greater than 5.5 points;

(b) increase from baseline of at least 20% in time to complete the 9-HPT; or

(c) increase from baseline of at least 20% in T25FWT;

and wherein the change from baseline is confirmed at least 12 weeks after the initial increase.

4. The method of any one of claims 1 to 3, wherein time to onset of cCDP12 in the subject is increased.

5. The method of any one of claims 1 to 4, wherein the risk of cCDP12 in the subject is reduced, and the annualized relapse rate of the subject is reduced, after beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof; wherein the risk reduction and annualized relapse rate reduction are independently greater than 25%.

6. A method of reducing the Annualized Relapse Rate (ARR) in a subject with relapsing multiple sclerosis (RMS) in need thereof, the method comprising administering to the subject about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

7. The method of claim 6, wherein the reduction of annualized relapse rate is greater than 25%.

8. A method of reducing the risk of experiencing cCDP12 in a subject with RMS, comprising administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein cCDP12 comprises the first occurence of a progression event in the subject after beginning of administration of fenebrutinib or a pharmaceutically acceptable salt thereof, wherein the progression event is confirmed at least 12 weeks after the initial disability progression.

10. A method of increasing time to onset of cCDP12 in a subject with RMS, comprising administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof, wherein time to onset of cCDP12 comprises the period from before beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof to the first occurrence of a progression event, wherein the progression event is confirmed at least 12 weeks after the initial disability progression.

11. The method of claim 9 or claim 10, wherein the progression event is one of:

(a) an increase from baseline in Expanded Disability Status Scale (EDSS) score of ≥1.0 point in a subject with a baseline EDSS score of ≤5.5 or an increase of ≥0.5 points in a subject with a baseline EDSS score of >5.5 (confirmed disability progression [CDP]);

(b) ≥20% increase from baseline in the Timed 25-Foot Walk Test (T25FWT); or

(c) ≥20% increase from baseline in time to complete the 9-Hole Peg Test (9-HPT).

12. The method of any one of claims 1 to 11, wherein the risk of experiencing cCDP12 is reduced by at least 25%, or the time to onset of cCDP12 is reduced by at least 25%, or a combination thereof.

13. The method of any one of claims 1 to 12, wherein the risk of the subject experiencing CDP12 is reduced.

14. The method of any one of claims 1 to 13, wherein the risk of the subject experiencing cCDP24 is reduced.

15. The method of any one of claims 1 to 14, wherein the number of T1 Gd+ lesions in the subject is reduced relative to a subject with RMS that is not administered fenebrutinib or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1 to 14, wherein the number of new and/or enlarging T2 hyperintense lesions in the subject is reduced relative to a subject with RMS that is not administered fenebrutinib or a pharmaceutically acceptable salt thereof.

17. The method of claim 15 or 16, wherein the relative reduction in lesions is reduced over 12 weeks, 24 weeks, 48 weeks, or 96 weeks after beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof.

18. The method of any one of claims 15 to 17, wherein the relative reduction is at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

19. The method of any one of claims 2 to 18, wherein the reduction is relative to another subject with RMS who is not administered fenebrutinib or a pharmaceutically acceptable salt thereof, and who is optionally administered a small molecule inhibitor of dihydroorotate dehydrogenase.

20. The method of any one of claims 1 to 19, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered orally.

21. The method of any one of claims 1 to 20, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered in the form of one or more tablets or capsules.

22. The method of any one of claims 1 to 21, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered in the form of two tablets twice daily, each tablet comprising about 100 mg fenebrutinib or an equivalent amount of a pharmaceutically acceptable salt thereof.

23. The method of any one of claims 1 to 22, wherein the free form of fenebrutinib is administered.

24. The method of any one of claims 2 to 7 or 12 to 23, wherein relapse comprises the subject experiencing a new or worsening neurological MS symptom, wherein the symptom persists for at least 24 hours, and wherein prior to experiencing the symptom the subject had a relatively stable or improving neurological state for at least 30 days.

25. The method of any one of claims 2 to 7 or 12 to 24, wherein relapse comprises an increase of at least one of the following:

increase of half a step (0.5 point) on the EDSS;

increase of two points on one functional systems score (FSS) selected from the group consisting of pyramidal, ambulation, cerebellar, brainstem, sensory, and visual; or

increase of one point on two or more of FSS selected from the group consisting of pyramidal, ambulation, cerebellar, brainstem, sensory, and visual.

26. The method of any one of claims 1 to 25, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject with RMS experienced at least two clinical relapses within the previous 2 years, or one clinical relapse within the previous 12 months; and has at least one T1Gd+ lesion on an MRI taken in the previous 12 months.

27. The method of any one of claims 1 to 26, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject with RMS has an EDSS score of 0-5.5.

28. The method of any one of claims 1 to 27, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject does not have an RMS disease duration of >10 years from the onset of symptoms combined with an EDSS score of <2.0

29. The method of any one of claims 1 to 28, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject does not have one or more of:

alanine transaminase (ALT) or (aspartate transaminase) AST >2×upper limit of normal (ULN);

total bilirubin greater than 1.5×ULN without a diagnosis of Gilbert syndrome; or

persisting elevations of serum amylase or lipase greater than 2×ULN.

30. The method of any one of claims 1 to 29, wherein the subject is not concomitantly administered a strong CYP3A4 inhibitor while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

31. The method of any one of claims 1 to 30, wherein the subject is not concomitantly administered a strong CYP3A4 inducer while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

32. The method of any one of claims 1 to 31, wherein the subject is not concomitantly administered a moderate CYP3A4 inducer while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

33. The method of any one of claims 1 to 32, wherein the subject is not concomitantly administered a CYP3A4 substrate with a narrow therapeutic window while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

34. A compound for use in the treatment of relapsing multiple sclerosis (RMS) in a subject in need thereof, wherein the compound is fenebrutinib or a pharmaceutically acceptable salt thereof, and wherein the treatment comprises administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

35. A compound for use in reducing Annualized Relapse Rate (ARR) and reducing the risk of experiencing cCDP12 in a subject with RMS, wherein the compound is fenebrutinib or a pharmaceutically acceptable salt thereof, and wherein reducing ARR and reducing the risk of experiencing cCDP12 comprises administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

36. The compound for use of claim 34 or 35, further comprising evaluating the onset of composite 12-week confirmed disability progression (cCDP12), wherein onset of cCDP12 comprises at least one of:

(a) an increase from baseline in EDSS score of at least 1.0 point in a subject with a baseline EDSS score of less than or equal to 5.5 points; or an increase from baseline in EDSS score of at least 0.5 point in a subject with a baseline EDSS score of greater than 5.5 points;

(b) increase from baseline of at least 20% in time to complete the 9-HPT; or

(c) increase from baseline of at least 20% in T25FWT;

and wherein the change from baseline is confirmed at least 12 weeks after the initial increase.

37. The compound for use of any one of claims 34 to 36, wherein time to onset of cCDP12 in the subject is increased.

38. The compound for use of any one of claims 34 to 37, wherein the risk of cCDP12 in the subject is reduced, and the annualized relapse rate of the subject is reduced, after beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof; wherein the risk reduction and annualized relapse rate reduction are independently greater than 25%.

39. A compound for use in reducing the annualized relapse rate in a subject with relapsing multiple sclerosis (RMS) in need thereof, wherein the compound is fenebrutinib or a pharmaceutically

acceptable salt thereof, and wherein the reduction comprises administering to the subject about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

40. The compound for use of claim 39, wherein the reduction of annualized relapse rate is greater than 25%.

41. A compound for use in reducing the risk of experiencing cCDP12 in a subject with RMS, wherein the compound is fenebrutinib or a pharmaceutically acceptable salt thereof, wherein reducing the risk comprises administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof.

42. The compound for use of claim 41, wherein cCDP12 comprises the first occurence of a progression event in the subject after beginning of administration of fenebrutinib or a pharmaceutically acceptable salt thereof, wherein the progression event is confirmed at least 12 weeks after the initial disability progression.

43. A compound for use in increasing time to onset of cCDP12 in a subject with RMS, wherein the compound is fenebrutinib or a pharmaceutically acceptable salt thereof, wherein increasing time to onset of cCDP12 comprises administering to the subject about 200 mg fenebrutinib twice daily, or an equivalent amount of a pharmaceutically acceptable salt thereof, wherein time to onset of cCDP12 comprises the period from before beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof to the first occurrence of a progression event, wherein the progression event is confirmed at least 12 weeks after the initial disability progression.

44. The compound for use of claim 42 or 43, wherein the progression event is one of:

(a) an increase from baseline in Expanded Disability Status Scale (EDSS) score of ≥1.0 point in a subject with a baseline EDSS score of ≤5.5 or an increase of ≥0.5 points in a subject with a baseline EDSS score of >5.5 (confirmed disability progression [CDP]);

(b) ≥20% increase from baseline in the Timed 25-Foot Walk Test (T25FWT); or

(c) ≥20% increase from baseline in time to complete the 9-Hole Peg Test (9-HPT).

45. The compound for use of any one of claims 34 to 44, wherein the risk of experiencing cCDP12 is reduced by at least 25%, or the time to onset of cCDP12 is reduced by at least 25%, or a combination thereof.

46. The compound for use of any one of claims 34 to 45, wherein the risk of the subject experiencing CDP12 is reduced.

47. The compound for use of any one of claims 34 to 46, wherein the risk of the subject experiencing cCDP24 is reduced.

48. The compound for use of any one of claims 34 to 47, wherein the number of T1 Gd+ lesions in the subject is reduced relative to a subject with RMS that is not administered fenebrutinib or a pharmaceutically acceptable salt thereof.

49. The compound for use of any one of claims 34 to 48, wherein the number of new and/or enlarging T2 hyperintense lesions in the subject is reduced relative to a subject with RMS that is not administered fenebrutinib or a pharmaceutically acceptable salt thereof.

50. The compound for use of claim 48 or 49, wherein the relative reduction in lesions is reduced over 12 weeks, 24 weeks, 48 weeks, or 96 weeks after beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof.

51. The compound for use of any one of 48 to 50, wherein the relative reduction is at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%.

52. The compound for use of any one of claims 35 to 51, wherein the reduction is relative to another subject with RMS who is not administered fenebrutinib or a pharmaceutically acceptable salt thereof, and who is optionally administered a small molecule inhibitor of dihydroorotate dehydrogenase.

53. The compound for use of any one of claims 34 to 52, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered orally.

54. The compound for use of any one of claims 34 to 53, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered in the form of one or more tablets or capsules.

55. The compound for use of any one of claims 34 to 54, wherein the fenebrutinib or pharmaceutically acceptable salt thereof is administered in the form of two tablets twice daily, each tablet comprising about 100 mg fenebrutinib or an equivalent amount of a pharmaceutically acceptable salt thereof.

56. The compound for use of any one of claims 34 to 55, wherein the free form of fenebrutinib is administered.

57. The compound for use of any one of claims 35 to 40 or 45 to 56, wherein relapse comprises the subject experiencing a new or worsening neurological MS symptom, wherein the symptom persists for at least 24 hours, and wherein prior to experiencing the symptom the subject had a relatively stable or improving neurological state for at least 30 days.

58. The compound for use of any one of claims 35 to 40 or 45 to 57, wherein relapse comprises an increase of at least one of the following:

increase of half a step (0.5 point) on the EDSS;

increase of two points on one functional systems score (FSS) selected from the group consisting of pyramidal, ambulation, cerebellar, brainstem, sensory, and visual; or

increase of one point on two or more of FSS selected from the group consisting of pyramidal, ambulation, cerebellar, brainstem, sensory, and visual.

59. The compound for use of any one of claims 34 to 58, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject with RMS experienced at least two clinical relapses within the previous 2 years, or one clinical relapse within the previous 12 months; and has at least one T1Gd+ lesion on an MRI taken in the previous 12 months.

60. The compound for use of any one of claims 34 to 59, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject with RMS has an EDSS score of 0-5.5.

61. The compound for use of any one of claims 34 to 60, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject does not have an RMS disease duration of >10 years from the onset of symptoms combined with an EDSS score of <2.0

62. The compound for use of any one of claims 34 to 61, wherein prior to beginning administration of fenebrutinib or a pharmaceutically acceptable salt thereof, the subject does not have one or more of:

alanine transaminase (ALT) or (aspartate transaminase) AST >2×upper limit of normal (ULN);

total bilirubin greater than 1.5×ULN without a diagnosis of Gilbert syndrome; or

persisting elevations of serum amylase or lipase greater than 2×ULN.

63. The compound for use of any one of claims 34 to 62, wherein the subject is not concomitantly administered a strong CYP3A4 inhibitor while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

64. The compound for use of any one of claims 34 to 63, wherein the subject is not concomitantly administered a strong CYP3A4 inducer while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

65. The compound for use of any one of claims 34 to 64, wherein the subject is not concomitantly administered a moderate CYP3A4 inducer while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

66. The compound for use of any one of claims 34 to 65, wherein the subject is not concomitantly administered a CYP3A4 substrate with a narrow therapeutic window while being administered about 200 mg fenebrutinib twice per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

67. A compound for use in the manufacture of a medicament for any of the methods of claims 1 to 33, wherein the compound is fenebrutinib or a pharmaceutically acceptable salt thereof.