

CLAIMS

What is claimed is:

1. A method of treating CBS deficiency in a subject, the method comprising:
 - a. determining a level of a metabolic indicator of disease severity or disease progression in the subject; and
 - b. administering to the subject a therapeutically effective amount of a pharmaceutical formulation comprising:
 - i. a drug substance comprising an isolated cystathionine β -synthase (CBS) protein comprising SEQ ID NO: 1;
 - ii. a PEG molecule covalently bound to the CBS protein; and
 - iii. a pharmaceutically acceptable excipient, diluent, or adjuvant;wherein the subject is a non-genetically defined patient having elevated tHcy levels or a non-genetically defined patient having CBS deficiency, and wherein the therapeutically effective amount of the pharmaceutical formulation comprises a dosage of the drug substance adjusted according to the level of the metabolic indicator of disease severity or disease progression in the subject.
2. The method of claim 1, wherein determining a level of a metabolic indicator of disease severity or disease progression in the subject comprises obtaining a blood or a blood plasma sample from the subject, measuring a level of one or more metabolic indicator of disease severity or disease progression in the sample, and comparing the level of the one or more metabolic indicator of disease severity or disease progression to a level of the same metabolic indicator in a control sample from a healthy subject.
3. The method of claim 1, wherein the dosage of the drug substance adjusted according to the level of the metabolic indicator of disease severity or disease progression in the subject comprises a low dose, a medium dose, or a high dose of 20NHS PEG-CBS.
4. The method of claim 3, wherein a low dose of 20NHS PEG-CBS comprises about 0.25 mg/kg to about 1.0 mg/kg 20NHS PEG-CBS.
5. The method of claim 3, wherein a medium dose of 20NHS PEG-CBS comprises about 0.5 mg/kg to about 1.5 mg/kg 20NHS PEG-CBS.
6. The method of claim 3, wherein a high dose of 20NHS PEG-CBS comprises about 1 mg/kg to about 2 mg/kg 20NHS PEG-CBS.

7. The method of claim 3, wherein a high dose of 20NHS PEG-CBS comprises about 2 mg/kg to about 10 mg/kg 20NHS PEG-CBS.
8. The method of any one of claims 1-7, wherein the metabolic indicator of disease severity or disease progression is total homocysteine (tHcy), methionine, creatinine, c-reactive protein, dimethylglycine, alanine aminotransferase, Protein C, aspartate aminotransferase (AST), anti-thrombin III, and/or apolipoprotein A.
9. The method of any one of claims 1-8, wherein the metabolic indicator of disease severity or progression is tHcy and a dosage of 20NHS PEG-CBS is administered to the subject according to an elevated-low, elevated-medium, or elevated-high tHcy level.
10. A method of improving cognitive function in a subject having elevated total plasma homocysteine (tHcy) levels, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical formulation comprising:
- a drug substance comprising an isolated cystathionine β -synthase (CBS) protein comprising SEQ ID NO: 1;
 - a PEG molecule covalently bound to the CBS protein; and
 - a pharmaceutically acceptable excipient, diluent, or adjuvant.
11. The method of claim 10, further comprising providing a cognitive or behavioral intervention.
12. The method of claim 10 or 11, wherein the cognitive or behavioral intervention comprises behavioral parent training (BPT) or behavioral classroom management (BCM).
13. A method of reducing skeletal fragility in a subject having elevated total plasma homocysteine (tHcy) levels, the method comprising administering to the subject a therapeutically effective amount of a pharmaceutical formulation comprising:
- a drug substance comprising an isolated cystathionine β -synthase (CBS) protein comprising SEQ ID NO: 1;
 - a PEG molecule covalently bound to the CBS protein; and
 - a pharmaceutically acceptable excipient, diluent, or adjuvant.
14. The method of claim 13, wherein skeletal fragility of the subject is assessed by bone mineral density determination.

15. The method of any one of claims 10-14, wherein the PEG molecule is ME-200GS.
16. The method of any one of claims 10-15, wherein the therapeutically effective amount comprises a dosage of about 0.25 mg/kg to about 10 mg/kg of the drug substance.
17. The method of claim 16, wherein the dosage is about 0.33 mg/kg of the drug substance.
18. The method of claim 16, wherein the dosage is about 0.66 mg/kg of the drug substance.
19. The method of claim 16, wherein the dosage is about 1.0 mg/kg of the drug substance.
20. The method of claim 16, wherein the dosage is about 1.5 mg/kg of the drug substance.
21. The method of any one of claims 10-20, further comprising administering one or more of vitamin B6, vitamin B12, folate, and betaine to the subject.
22. The method of any one of claims 10-21, wherein the subject is on a methionine (Met)-restricted diet.
23. The method of claim 22, further comprising terminating or relaxing the methionine restricted diet.
24. The method of any one of claims 10-23, further comprising administering an anti-platelet agent.
25. The method of claim 24, wherein the anti-platelet agent is a warfarin blood thinner or an anti-coagulation agent.
26. The method of any one of claims 10-25, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is performed about once every 3 days.

27. The method of any one of claims 10-25, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is performed about once per day.

28. The method of any one of claims 10-25, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is performed about twice per day.

29. The method of any one of claims 10-25, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is performed about once per week.

30. The method of any one of claims 10-25, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is performed about twice per week.

31. The method of any one of claims 10-30, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is repeated for about 6 weeks.

32. The method of any one of claims 10-30, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is repeated for about 3 months.

33. The method of any one of claims 10-30, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is repeated for about 6 months.

34. The method of any one of claims 10-30, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is repeated for longer than 6 months.

35. The method of any one of claims 10-30, wherein the administering a therapeutically effective amount of the pharmaceutical formulation is repeated for the remaining life span of the subject.

36. The method of any one of claims 10-35, wherein the elevated total plasma homocysteine (tHcy) levels in the subject comprise tHcy levels greater than about 5 $\mu\text{mol/L}$.

37. The method of any one of claims 10-36, wherein the elevated total plasma homocysteine (tHcy) levels in the subject comprise tHcy levels greater than about 10 $\mu\text{mol/L}$.
38. The method of any one of claims 10-37, wherein the elevated total plasma homocysteine (tHcy) levels in the subject comprise tHcy levels greater than about 15 $\mu\text{mol/L}$.
39. The method of any one of claims 10-38, wherein the subject having elevated total plasma homocysteine (tHcy) levels is a genetically-defined HCU patient.
40. The method of any one of claims 10-38, wherein the subject having elevated total plasma homocysteine (tHcy) levels is a non-genetically defined patient having elevated tHcy levels or having CBS deficiency.