**CLAIMS**

~~What is claimed is:~~

1. Use of a pharmaceutical formulation in the manufacture of a medicament for the ~~A method of~~ treatment of~~ing~~ CBS deficiency in a subject, wherein:

a. the ~~the method comprising~~treatment of~~ing~~ CBS deficiency comprises:

~~a~~i. determining a level of a metabolic indicator of disease severity or disease progression in the subject; ~~and~~

~~b~~ii. ~~administering to the subject a therapeutically effective amount of a the pharmaceutical formulation, 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;~~

b. the pharmaceutical formulation ~~comprising~~comprises:

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; and

c. ~~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 which 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 is to be administered to the subject.

2. The ~~method~~ use 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~~ use 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~~ use 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~~ use 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~~ use 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~~ use 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~~ use 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~~ use 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 to be administered to the subject according to an elevated-low, elevated-medium, or elevated-high tHcy level.

10. Use of a pharmaceutical formulation in the manufacture of a medicament for ~~A method of~~ improving cognitive function in a subject having elevated total plasma homocysteine (tHcy) levels, wherein ~~the method comprising administering to the subject a therapeutically effective amount of a~~ the pharmaceutical formulation ~~comprising~~comprises:

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~~ use of claim 10, ~~further comprising providing~~wherein the subject is to be provided 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~~12. Use of a pharmaceutical formulation in the manufacture of a medicament for ~~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~~wherein the pharmaceutical formulation ~~comprising~~comprises:

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~~13. The ~~method~~ use of any one of claims 10-~~14~~12, wherein the PEG molecule is ME-200GS.

~~16~~14. The ~~method~~ use of any one of claims 10-~~15~~13, 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~~15. The ~~method~~ use of any one of claims 10-~~20~~15, ~~further comprising administering~~wherein the subject is to be administered one or more of vitamin B6, vitamin B12, folate, and betaine ~~to the subject~~.

~~22~~16. The ~~method~~ use of any one of claims 10-~~21~~15, 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~~17. The ~~method~~ use of any one of claims 10-~~23~~16, ~~further comprising administering~~ wherein the subject is to be administered 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~~18. The ~~method~~ use of any one of claims 10-~~25~~17, wherein ~~the administering a therapeutically effective amount of~~ the pharmaceutical formulation ~~is performed~~is to be administered to the subject (a) about once every 3 days; (b) about once per day; (c) about twice per day; (d) about once per week; (e) about twice per week; (f) for about 6 weeks; (g) for about 3 months; (h) for about 6 months; (i) for longer than 6 months; or (j) for the remaining lifespan of the subject.

~~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~~19. The ~~method~~ use of any one of claims 10-~~35~~18, wherein the elevated total plasma homocysteine (tHcy) levels in the subject comprise tHcy levels greater than about 5 µmol/L; greater than about 10 µmol/L; or greater than about 15 µmol/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 µmol/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 µmol/L.~~

~~39~~20. The ~~method~~ use of any one of claims 10-~~38~~19, wherein the subject having elevated total plasma homocysteine (tHcy) levels is (a) a genetically-defined HCU patient; or (b) a non-genetically defined patient having elevated tHcy levels or having CBS deficiency.

~~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.~~