CLAIMS

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

a. the treatment of CBS deficiency comprises:

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

b. the pharmaceutical formulation 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. 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 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 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 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 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 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 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 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 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 improving cognitive function in a subject having elevated total plasma homocysteine (tHcy) levels, wherein the pharmaceutical formulation 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 use of claim 10, wherein the subject is to be provided a cognitive or behavioral intervention.

12. Use of a pharmaceutical formulation in the manufacture of a medicament for reducing skeletal fragility in a subject having elevated total plasma homocysteine (tHcy) levels, wherein the pharmaceutical formulation 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.

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

14. The use of any one of claims 10-13, wherein the therapeutically effective amount comprises a dosage of about 0.25 mg/kg to about 10 mg/kg of the drug substance.

15. The use of any one of claims 10-15, wherein the subject is to be administered one or more of vitamin B6, vitamin B12, folate, and betaine.

16. The use of any one of claims 10-15, wherein the subject is on a methionine (Met)-restricted diet.

17. The use of any one of claims 10-16, wherein the subject is to be administered an anti-platelet agent.

18. The use of any one of claims 10-17, wherein the pharmaceutical formulation 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.

19. The use of any one of claims 10-18, 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.

20. The use of any one of claims 10-19, 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.