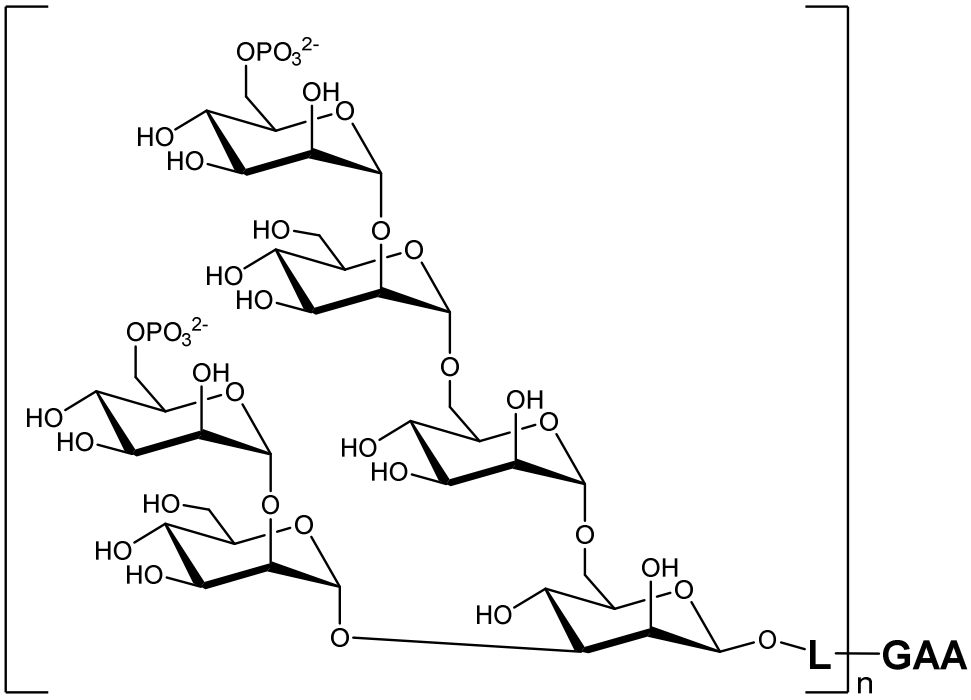
CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition comprising ~~A method for treating an infantile-onset Pompe disease (IOPD), comprising administering to a human individual in need thereof a pharmaceutical composition comprising~~ an oligosaccharide-protein conjugate and a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating infantile-onset Pompe disease (IOPD) in a human individual, wherein the oligosaccharide-protein conjugate has a structure of Formula I:



(I),

wherein GAA is acid α-glucosidase, L is a chemical linker connecting the oligosaccharide and the GAA, and n is 1 to 10, and

wherein the pharmaceutical composition is to be administered at a dose of about 20 mg/kg to about 40 mg/kg.

2. The ~~method~~use of claim 1, wherein the pharmaceutical composition is to be administered at a dose of about 20 mg/kg or about 40 mg/kg.

~~3. The method of claim 1, wherein the pharmaceutical composition is administered at a dose of about 40 mg/kg.~~

3.~~4.~~ The ~~method~~use of claim 1 or 2~~any one of claims 1-3~~, wherein the pharmaceutical composition is to be administered:

a. to the individual once every two weeks;

b. intravenously; and/or

c. administered to the individual for at least about 25 weeks.

~~5. The method of any one of claims 1-4, wherein the pharmaceutical composition is administered intravenously.~~

~~6. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered to the individual for at least about 25 weeks.~~

4.~~7.~~ The ~~method~~use of any one of claims 1-3~~6~~, wherein the pharmaceutical composition is reconstituted from a lyophilized formulation comprising the oligosaccharide-protein conjugate.

5.~~8.~~ The ~~method~~use of claim 4~~7~~, wherein the pharmaceutically acceptable carrier comprises a sugar that is not degraded by GAA, optionally wherein the sugar that is not degraded by GAA is mannitol.

~~9. The method of claim 8, wherein the sugar that is not degraded by GAA is mannitol.~~

6.~~10.~~ The ~~method~~use of claim 4 or 5~~any one of claims 7-9~~, wherein the pharmaceutically acceptable carrier further comprises glycine and/or histidine.

~~11. The method of any one of claims 7-10, wherein the pharmaceutically acceptable carrier comprises histidine.~~

7.~~12.~~ The ~~method~~use of any one of claims 4-6~~7-11~~, wherein the pharmaceutical composition has a pH of about 6.2.

8.~~13.~~ The ~~method~~use of any one of claims 4-7~~7-12~~, wherein the pharmaceutically acceptable carrier comprises about 10-50 mM histidine, about 0.25-2% glycine, about 1-4% mannitol, and about 0.005-0.05% polysorbate 80.

9.~~14.~~ The ~~method~~use of claim 8~~13~~, wherein the pharmaceutically acceptable carrier comprises about 10 mM histidine, about 2% glycine, about 2% mannitol, and about 0.01% polysorbate 80.

10.~~15.~~ The ~~method~~use of any one of claims 1-9~~14~~, wherein the individual:

a. has cardiomyopathy at the time of diagnosis in the first year of life;

b. has arrhythmia;

c. has cardiomegaly;

d. is 18 years old or younger;

e. is 6 months old or younger; and/or

f. has not received treatment with a recombinant GAA.

~~16. The method of claim 15, wherein the individual has arrhythmia.~~

~~17. The method of claim 15, wherein the individual has cardiomegaly.~~

~~18. The method of any one of claims 1-17, wherein the individual is 18 years old or younger.~~

~~19. The method of claim 18, wherein the individual is 6 months old or younger.~~

11.~~20.~~ The ~~method~~use of any one of claims 1-10~~18~~, wherein the individual has received at least 6 months of treatment with a recombinant GAA, optionally, wherein the individual shows clinical decline after treatment with the recombinant GAA, wherein the clinical decline is determined by assessing one or more parameters selected from the group consisting of respiratory functions, motor skills and cardiac parameters.

~~21. The method of claim 20, wherein the individual shows clinical decline after treatment with the recombinant GAA, wherein the clinical decline is determined by assessing one or more parameters selected from the group consisting of respiratory functions, motor skills and cardiac parameters.~~

12.~~22.~~ The ~~method~~use of claim 11~~20~~, wherein the individual has suboptimal clinical response to treatment with the recombinant GAA, wherein the clinical response is determined by assessing one or more parameters selected from the group consisting of respiratory functions, motor skills and cardiac parameters.

~~23. The method of any one of claims 1-19, wherein the individual has not received treatment with a recombinant GAA.~~

13.~~24.~~ The ~~method~~use of claim 11 or 12~~any one of claims 20-23~~, wherein the recombinant GAA is alglucosidase alfa.

14.~~25.~~ The ~~method~~use of any one of claims 1-13~~24~~, wherein the individual is cross-reactive immunologic material (CRIM)-negative or the individual is CRIM-positive.

~~26. The method of any one of claims 1-24, wherein the individual is CRIM-positive~~.

15.~~27.~~ The ~~method~~use of any one of claims 1-14~~26~~, further comprising administering to the individual an effective amount of methotrexate, optionally, wherein the effective amount of methotrexate is administered in a single cycle or in three cycles.

~~28. The method of claim 27, wherein the effective amount of methotrexate is administered in a single cycle or in three cycles.~~

16.~~29.~~ The ~~method~~use of claim 15~~27 or 28,~~ further comprising administering to the individual an effective amount of an additional immune tolerance induction therapy, optionally, wherein the additional immune tolerance induction therapy comprises rituximab and intravenous immunoglobulin (IVIG).

~~30. The method of claim 29, wherein the additional immune tolerance induction therapy comprises rituximab and intravenous immunoglobulin (IVIG).~~

17.~~31.~~ The ~~method~~use of any one of claims 1-16~~30~~, wherein:

a. the individual has decreasing level of antidrug antibody (ADA) against the oligosaccharide-protein conjugate over time;

b. creatine kinase (CK) level of the individual decreases by at least about 100 IU/L when measured after at least about 25 weeks of treatment;

c. urinary hexose tetrasaccharide (Hex4) level of the individual decreases by at least about 10 mmol/mol when measured after at least about 25 weeks of treatment;

d. Gross Motor Function Measure (GMFM-88) score of the individual increases by at least 5% when measured after at least about 25 weeks of treatment; and/or

e. the individual shows improvement or stabilization of one or more parameters selected from the group consisting of respiratory functions, motor skills, cardiac parameters and eyelid positions.

~~32. The method of any one of claims 1-31, wherein creatine kinase (CK) level of the individual decreases by at least about 100 IU/L when measured after at least about 25 weeks of treatment.~~

~~33. The method of any one of claims 1-32, wherein urinary hexose tetrasaccharide (Hex4) level of the individual decreases by at least about 10 mmol/mol when measured after at least about 25 weeks of treatment.~~

~~34. The method of any one of claims 1-33, wherein Gross Motor Function Measure (GMFM-88) score of the individual increases by at least 5% when measured after at least about 25 weeks of treatment.~~

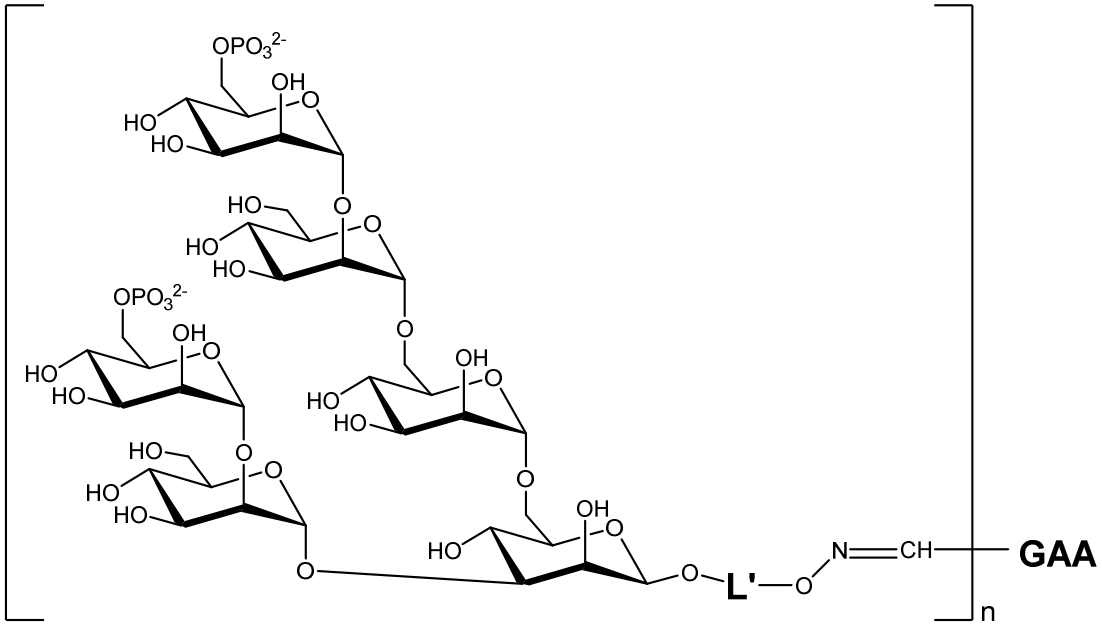
~~35. The method of any one of claims 1-34, wherein the individual shows improvement or stabilization of one or more parameters selected from the group consisting of respiratory functions, motor skills, cardiac parameters and eyelid positions.~~

18.~~36.~~ The ~~method~~use of claim 17~~35~~, wherein the improvement or stabilization is assessed based on one or more parameters selected from the group consisting of Alberta Infant Motor Scale (AIMS) score, Pompe-Pediatric Evaluation of Disability Inventory (PEDI) functional skills scale, Echocardiographic (ECHO)-left ventricular mass (LVM) Z-score, ECHO LVMI score, Gross Motor Function Classification System-Expanded and Revised (GMFCS-E&R) score, Quick Motor Function Test, 6 Minute Walk test (6MWT), interpalpebral fissure distance (IPFD), margin reflex distance-1 (MRD-1), margin pupil distance (MPD), onset of ptosis, and use of respiratory support.

~~37. The method of claim 36, wherein the improvement or stabilization is assessed based on Pompe-PEDI functional skills scale.~~

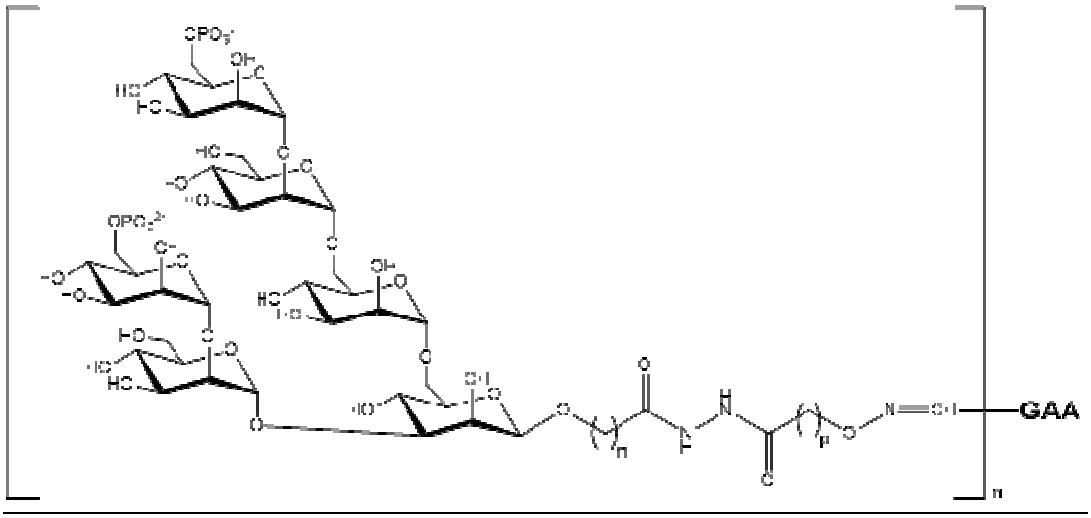
~~38. The method of claim 36, wherein the improvement or stabilization is assessed based on ECHO-LVM-Z-score.~~

19.~~39.~~ The ~~method~~use of any one of claims 1-18~~38~~, wherein the oligosaccharide-protein conjugate has a structure of Formula II:



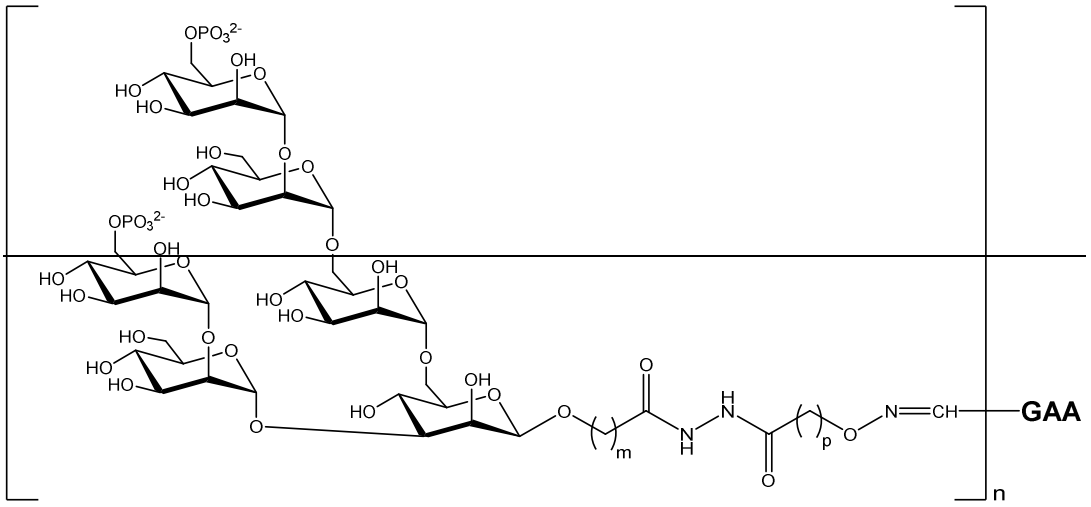
(II),

wherein GAA is acid a-glucosidase, L' is a chemical linker, and n is 1 to 10, or wherein the oligosaccharide-protein conjugate has a structure of Formula (III):



wherein GAA is acid a-glucosidase, n is 1 to 10, and wherein m and p are independently chosen from integers ranging from 1 to 10, optionally, wherein m is 3, p is 1, and/or n is 5-7.

~~40. The method of claim 39, wherein the oligosaccharide-protein conjugate has a structure of Formula III:~~



~~(III),~~

~~wherein GAA is acid a-glucosidase, n is 1 to 10, and wherein m and p are independently chosen from integers ranging from 1 to 10.~~

~~41. The method of claim 40, wherein m is 3 and p is 1.~~

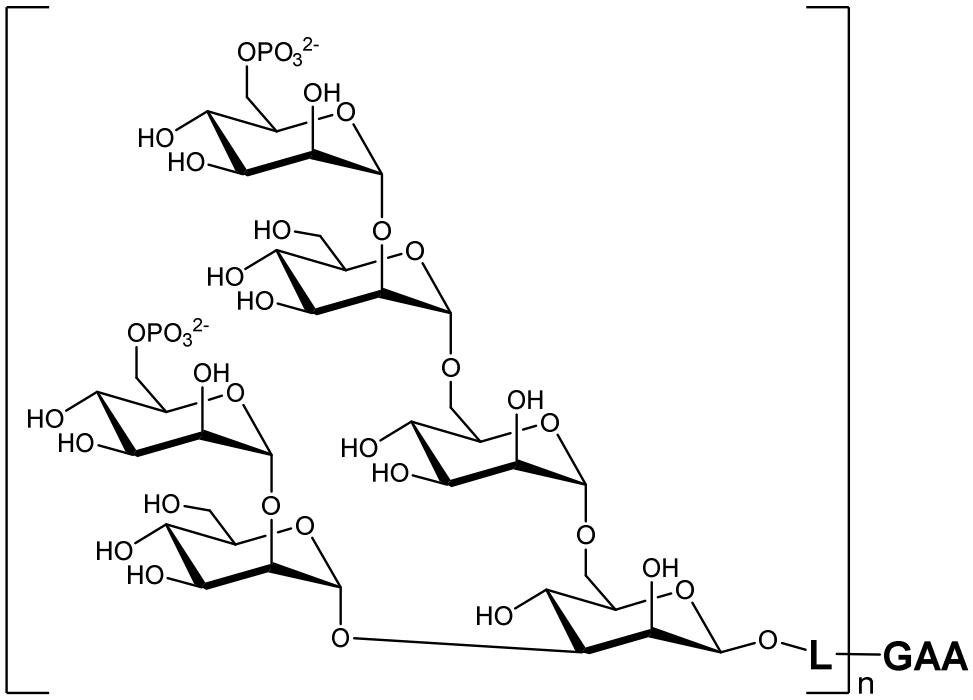
~~42. The method of claim 40 or 41, wherein n is 5-7.~~

20.~~43.~~ The ~~method~~use of any one of claims 1-19~~42~~, wherein the GAA is a human GAA produced in Chinese hamster ovary (CHO) cells.

21.~~44.~~ The ~~method~~use of claim 20~~43~~, wherein the human GAA has glycoform alfa and/or wherein the oligosaccharide-protein conjugate is avalglucosidase alfa.

~~45. The method of claim 44, wherein the oligosaccharide-protein conjugate is avalglucosidase alfa.~~

22.~~46.~~ A formulation comprising: (a) an oligosaccharide-protein conjugate; and (b) one or more cryoprotectants comprising a sugar that is not degraded by acid α-glucosidase; wherein the oligosaccharide-protein conjugate has a structure of Formula I:



(I),

wherein GAA is acid a-glucosidase, L' is a chemical linker, and n is 1 to 10.

~~47. The formulation of claim 46, wherein the sugar is mannitol.~~

~~48. The formulation of claim 47, comprising about 1-4% (w/w) mannitol.~~

~~49. The formulation of any one of claims 46-48, wherein the one or more cryoprotectants further comprises an amino acid.~~

~~50. The formulation of claim 49, wherein the amino acid is glycine.~~

~~51. The formulation of claim 50, comprising about 0.25-2% (w/w) glycine.~~

~~52. The formulation of any one of claims 46-51, wherein the one or more cryoprotectants further comprises a surfactant.~~

~~53. The formulation of claim 52, wherein the surfactant is polysorbate 80.~~

54. The formulation of claim 53, comprising about 0.005-0.05% (w/w) polysorbate 80.

55. The formulation of any one of claims 46-54, further comprising a buffering agent.

56. The formulation of claim 55, wherein the buffering agent is histidine.

57. The formulation of claim 56, comprising about 10-50 mM histidine.

58. The formulation of claim 57, comprising about comprising 10 mM histidine, about 2% glycine, about 2% mannitol, and about 0.01% polysorbate 80.

59. The formulation of any one of claims 46-58, wherein the formulation is a lyophilized formulation.

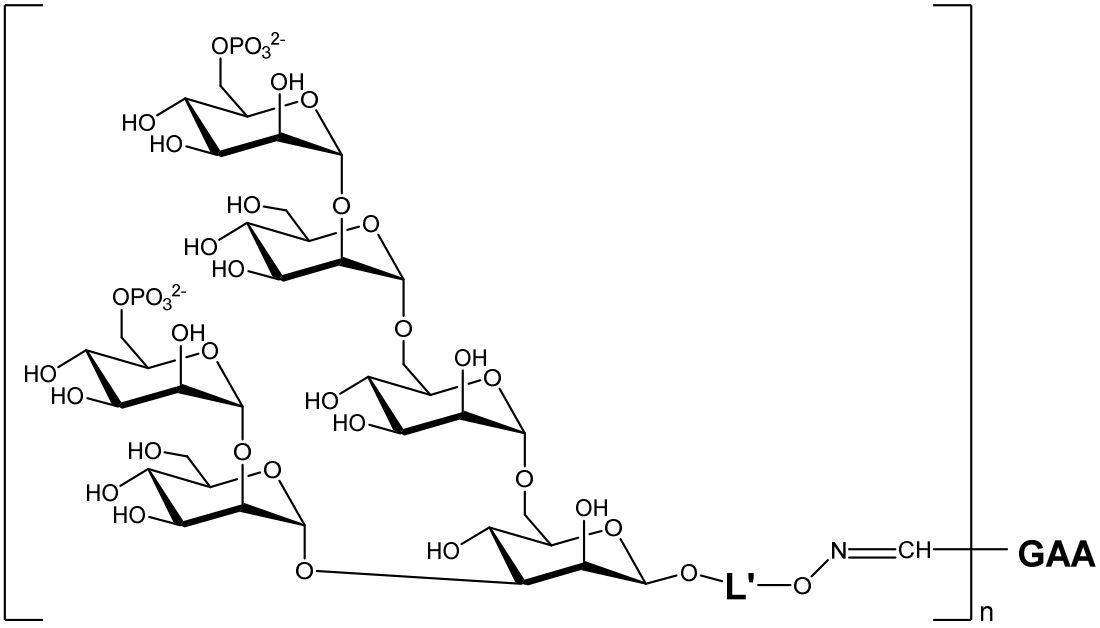
60. The formulation of any one of claims 46-58, wherein the formulation is a pre-lyophilized or reconstituted liquid formulation.

61. The formulation of claim 60, wherein the pH of the formulation is about 5.5 to about 6.5.

62. The formulation of claim 61, wherein the pH of the formulation is about 6.2.

63. The formulation of any one of claims 46-62, wherein the formulation comprises about 5-10 mg/mL of the oligosaccharide-protein conjugate.

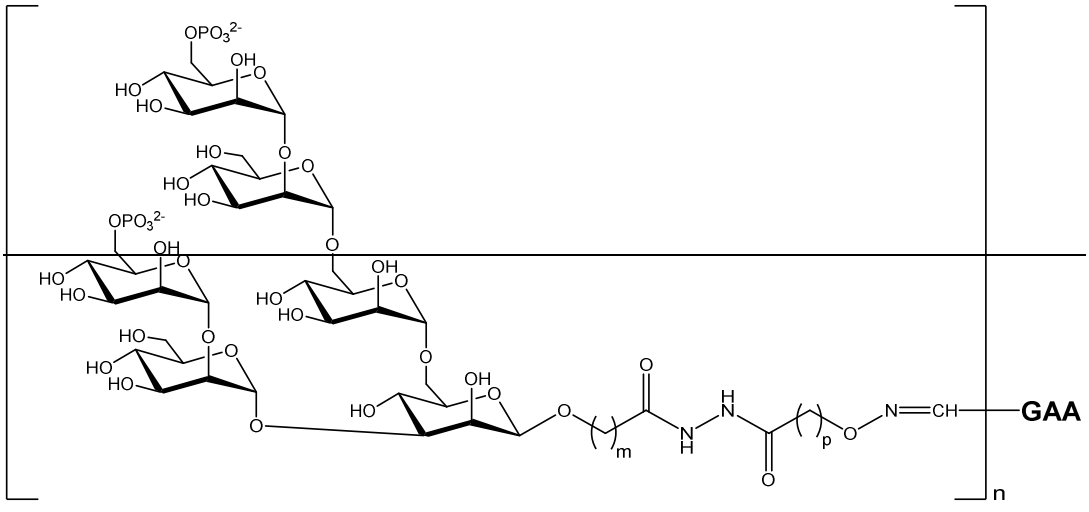
64. The formulation of any one of claims 46-63, wherein the oligosaccharide-protein conjugate a structure of Formula
II:



(II),

wherein GAA is acid a-glucosidase, L' is a chemical linker, and n is 1 to 10.

65. The formulation of claim 64, wherein the oligosaccharide-protein conjugate has a structure of Formula III:



(III),

wherein GAA is acid a-glucosidase, n is 1 to 10, and wherein m and p are independently chosen from integers ranging from 1 to 10.

66. The formulation of claim 65, wherein m is 3 and p is 1.

67. The formulation of claim 65 or 66, wherein n is 5-7.

~~68. The formulation of any one of claims 46-67, wherein the GAA is a human GAA produced in Chinese hamster ovary (CHO) cells.~~

~~69. The formulation of claim 68, wherein the human GAA has glycoform alfa.~~

~~70. The formulation of claim 69, wherein the oligosaccharide-protein conjugate is avalglucosidase alfa.~~

23.~~71.~~ An article of manufacture comprising a container comprising the formulation of claim 22~~any one of claims 46-70~~.

24.~~72.~~ The article of manufacture of claim 23~~71~~, wherein the container is a vial, optionally, wherein the formulation is a lyophilized formulation.

~~73. The article of manufacture of claim 72, wherein the formulation is a lyophilized formulation.~~

25.~~74.~~ ~~A method~~Use of ~~treating Pompe disease, comprising administering to a human individual in need thereof~~ an effective amount of a pharmaceutical composition comprising the formulation of claim 22~~any one of claims 46-70~~, in the manufacture of a medicament for treating Pompe disease in a human individual, optionally, wherein the Pompe disease is IOPD.

~~75. The method of claim 74, wherein the Pompe disease is IOPD.~~

26.~~76.~~ A kit comprising the formulation of claim 22~~any one of claims 46-70~~, optionally, further comprising instructions for use in treating Pompe disease.

~~77. The kit of claim 76, further comprising instructions for use in treating Pompe disease.~~