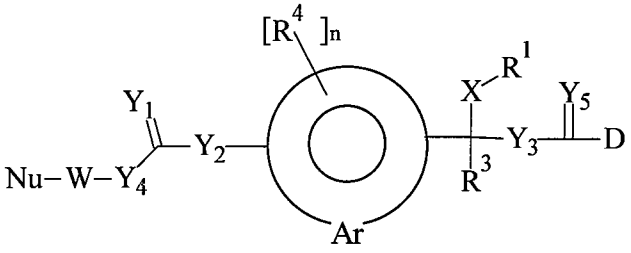
Claims

1. A pharmaceutical formulation comprising a polymeric human growth hormone (hGH) prodrug or a pharmaceutically acceptable salt thereof and at least one excipient, wherein the pharmaceutical formulation is a dry formulation and comprises from 1 to 99.9% (w/w) of the prodrug of formula (Ia)



(Ia),

wherein

-D is a hGH moiety connected to the rest of the molecule through an amine functional group;

n is 0, 1, 2, 3, or 4;

-X- is a chemical bond or a spacer;

$=Y_1$ is selected from the group consisting of =O and =S;

$-Y_2-$ is selected from the group consisting of -O- and -S-;

$-Y_3-$, $-Y_5-$ are independently of each other selected from the group consisting of -O- and -S-;

$-Y_4-$ is selected from the group consisting of -O-, $-NR^5-$ and $-C(R^6R^{6a})-$;

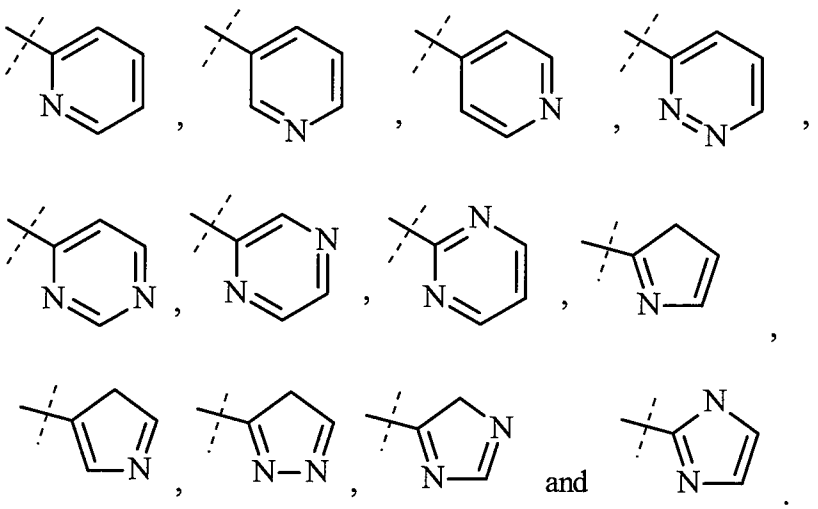
$-R^1$ is is a water-soluble PEG-based moiety comprising at least 40% PEG having a molecular weight ranging from 30 to 50 kDa;

$-R^3$, $-R^5$, $-R^6$, $-R^{6a}$ are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

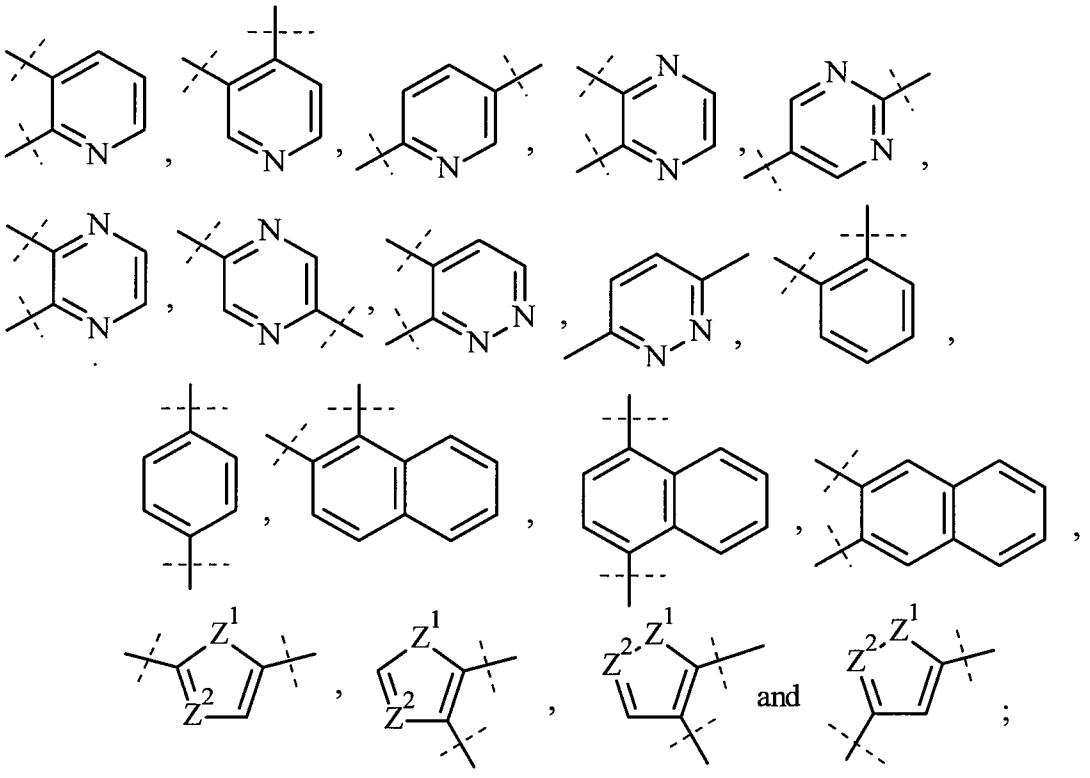
$-R^4$ is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-membered carbopolycyclyl, 3- to 10-membered heterocyclyl, $-C(O)-$, $-C(O)N(R^7)-$, -O-, -S- and $-N(R^7)-$;

-Nu is a nucleophile selected from the group consisting of -N(R^7R^{7a}), -N(R^7OH), -N(R^7)-N($R^{7a}R^{7b}$), -S(R^7),-COOH,



-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the rest of the prodrug,

-Z^1- is selected from the group consisting of -O-, -S- and -N(R^7)-, and

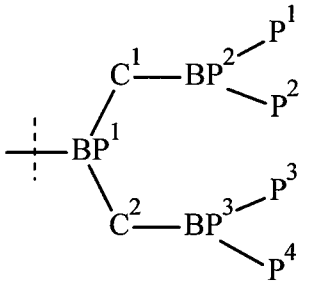
-Z^2- is -N(R^7)-; and

-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; and

wherein the prodrug of formula (Ia) is optionally further substituted.

2. The pharmaceutical formulation of claim 1, wherein $-R^1$ has a molecular weight ranging from 35 to 45 kDa.

3. The pharmaceutical formulation of claim 1 or 2, wherein $-R^1$ comprises a moiety of formula (II)



(II),

wherein

$-BP^1<$, $-BP^2<$, $-BP^3<$ are independently of each other selected from the group consisting of $-N<$ and $-C(R^8)<$;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

$-P^1$, $-P^2$, $-P^3$, $-P^4$ are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 8 to 12 kDa;

$-C^1-$, $-C^2-$ are independently of each other selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-S(O)N(R^{10})-$, $-S(O)_2-$, -S(O)-, $-N(R^{10})S(O)_2N(R^{10a})-$, -S-, $-N(R^{10})-$, $-OC(OR^{10})(R^{10a})-$, $-N(R^{10})C(O)N(R^{10a})-$, and $-OC(O)N(R^{10})-$;

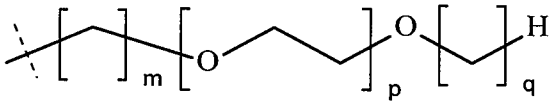
each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more R^9, which are the same or different;

each R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), $-COOR^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)N(R^{11}R^{11a})$, $-S(O)_2N(R^{11}R^{11a})$,

$-S(O)N(R^{11}R^{11a})$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-N(R^{11})S(O)_2N(R^{11a}R^{11b})$, $-SR^{11}$, $-N(R^{11}R^{11a})$, $-NO_2$, $-OC(O)R^{11}$, $-N(R^{11})C(O)R^{11a}$, $-N(R^{11})S(O)_2R^{11a}$, $-N(R^{11})S(O)R^{11a}$, $-N(R^{11})C(O)OR^{11a}$, $-N(R^{11})C(O)N(R^{11a}R^{11b})$, $-OC(O)N(R^{11}R^{11a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each R^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

4. The pharmaceutical formulation of claim 3, wherein P^1, P^2, P^3 and P^4 are independently of each other of formula (IIb)



(IIb),

wherein

the dashed line indicates attachment the remainder of R^1, i.e. to BP^2 or BP^3, respectively,

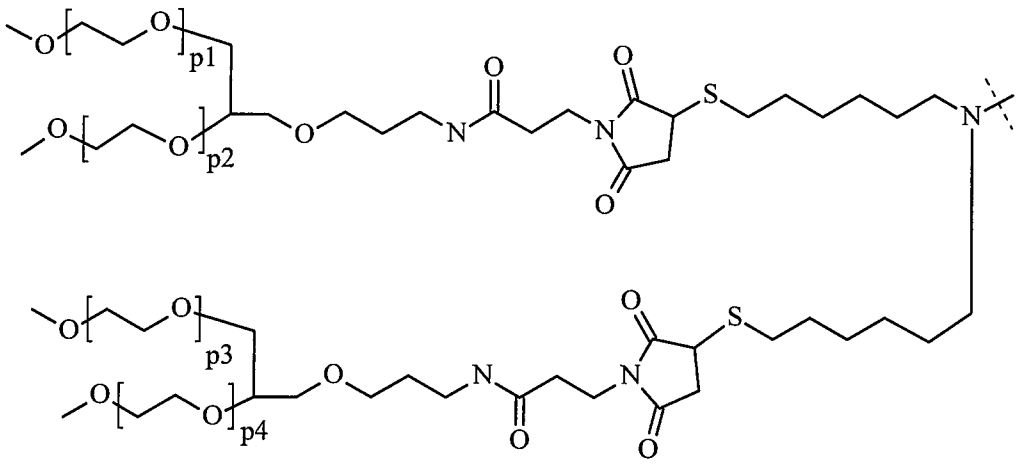
m is 0 or 1,

p is an integer ranging from 180 to 270, and

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

5. The pharmaceutical composition of claim 4, wherein p is an integer ranging from 220 to 240.

6. The pharmaceutical formulation of any one of claims 1 to 5, wherein $-R^1$ comprises a moiety of formula (IIc):

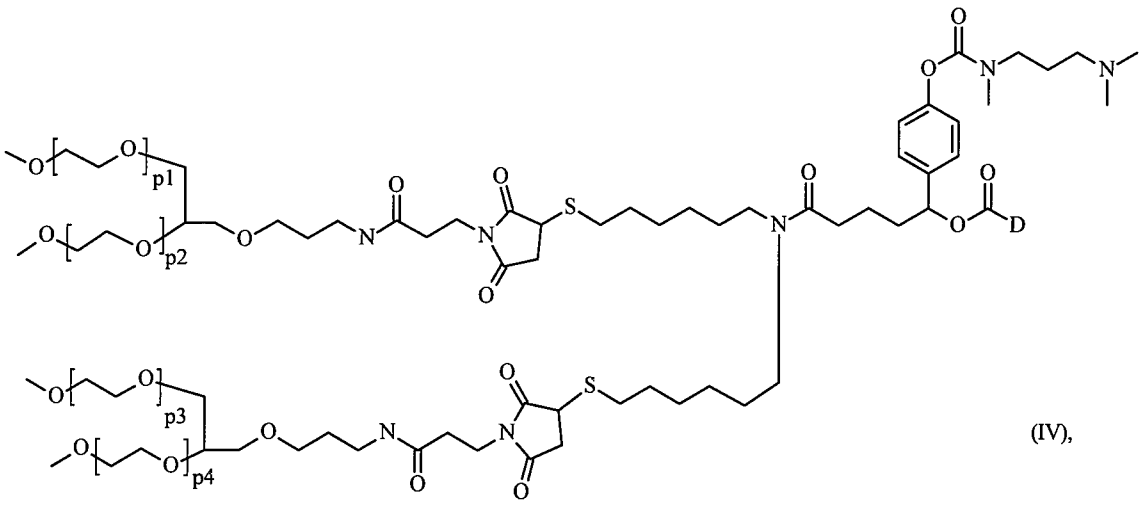


(IIc),

wherein

p1, p2, p3, p4 are independently an integer ranging from 180 to 270.

7. The pharmaceutical formulation of any one of claims 1 to 6, wherein the polymeric hGH prodrug is of formula (IV)



(IV),

wherein

D is a hGH moiety connected to the rest of the molecule through an amine functional group; and

p1, p2, p3, p4 are independently an integer ranging from 180 to 270.

8. The pharmaceutical composition of claim 6 or 7, wherein p1, p2, p3, p4 are independently an integer ranging from 200 to 250.

9. The pharmaceutical composition of any one of claims 6 to 8, wherein p1, p2, p3, p4 are independently an integer ranging from 210 to 240.

10. The pharmaceutical composition of any one of claims 6 to 9, wherein p1, p2, p3, p4 are independently an integer ranging from 220 to 240.

11. The pharmaceutical formulation of any one of claims 1 to 10, wherein the pharmaceutical formulation comprises from 9 to 71% (w/w) of the polymeric hGH prodrug.

12. The pharmaceutical formulation of any one of claims 1 to 11, wherein the pharmaceutical formulation comprises from 32 to 34% (w/w) or 50 to 54% (w/w) of the polymeric hGH prodrug.

13. The pharmaceutical formulation of any one of claims 1 to 12, wherein the dry formulation is obtained by a process comprising the steps of

(a) Providing a liquid formulation comprising

polymeric hGH prodrug	3-300 mg/ml
succinic acid	5-50 mM
optionally trehalose dihydrate	25-150 mg/ml

and having a pH ranging from pH 4.0 to pH 6.0 which is titrated using a suitable buffer; and wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 10; and

(b) Drying the liquid formulation of step (a).

14. The pharmaceutical formulation of any one of claims 1 to 13, wherein the dry formulation comprises based on the total weight of the formulation:

polymeric hGH prodrug	14-65% (w/w)
succinic acid	0.5-2.5% (w/w)
trehalose dihydrate	31-84% (w/w)
Tris	0.4-4% (w/w)

wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 10.

15. A method of reconstituting the pharmaceutical formulation of any one of claims 1 to 14, wherein the method comprises the step of

- contacting the dry pharmaceutical formulation of any one of claims 1 to 14 with a reconstitution solution.

16. A reconstituted formulation obtainable from the method of claim 15.

17. The reconstituted formulation of claim 16, wherein the reconstituted formulation comprises

polymeric hGH prodrug	3-300 mg/ml
succinic acid	5-50 mM
trehalose dihydrate	25-150 mg/ml
Tris	1-50 mM

and has a pH ranging from pH 4.0 to pH 6.0; and wherein the polymeric hGH prodrug is the prodrug of any one of claims 1 to 10.

18. The pharmaceutical formulation of any one of claims 1 to 14 or the reconstituted formulation of claim 16 or 17 for use as a medicament.

19. Use of the pharmaceutical formulation of any one of claims 1 to 14 or the reconstituted formulation of claim 16 or 17 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of growth hormone deficiency in children, idiopathic short stature, short stature homeobox gene mutations, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, children born small for gestational age, chronic renal insufficiency, growth hormone deficiency in adults, wasting due to HIV or AIDS or other malignancies, short bowel syndrome, sarcopenia, and frailty.

20. The use as claimed in claim 19, wherein the medicament is to be administered via topical, enteral or parenteral administration or by methods of external application, injection or infusion, including intraarticular, periarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, intracapsular, intraorbital, intravitreal, intratympanic, intravesical, intracardiac, transtracheal, subcuticular, subcapsular, subarachnoid, intraspinal, intraventricular, intrasternal injection or infusion, direct delivery to the brain via implanted device allowing delivery of the invention or the like to brain tissue or brain fluids, direct intracerebroventricular injection or infusion, injection or infusion into brain or brain associated regions, injection into the subchoroidal space, retro-orbital injection and ocular instillation.