Claims

1. A dry pharmaceutical formulation, wherein the pharmaceutical formulation comprises a CNP conjugate, a buffering agent and a bulking agent ~~and,~~ wherein the CNP conjugate comprises a CNP moiety that is covalently and reversibly conjugated via a side chain of an amino acid residue of its ring moiety or a backbone of its ring moiety to a polymeric moiety, the buffering agent is succinic acid, and the bulking agent is trehalose.

~~2. The dry pharmaceutical formulation of claim 1, wherein the buffering agent is selected from the group consisting of succinic acid, citric acid, lactic acid, acetic acid, glutamic acid, fumaric acid, aspartic acid, glutaric acid, phosphoric acid, histidine, gluconic acid, tartaric acid, malic acid and mixtures thereof.~~

~~3. The dry pharmaceutical formulation of claim 1 or 2, wherein the buffering agent is succinic acid.~~

~~4. The dry pharmaceutical formulation of any one of claims 1 to 3, wherein the bulking agent is selected from the group consisting of trehalose, mannitol, sucrose, raffinose, gelatin, lactose, dibasic calcium phosphate, sorbitol, xylitol, glycine, histidine, hydroxyethylstarch, dextrose, dextran, propylene glycol and mixtures thereof.~~

~~5. The dry pharmaceutical formulation of any one of claims 1 to 4, wherein the bulking agent is selected from the group consisting of trehalose, sucrose and glycine.~~

~~6. The dry pharmaceutical formulation of any one of claims 1 to 5, wherein the bulking agent is trehalose.~~

~~7~~2. The dry pharmaceutical formulation of ~~any one of~~ claim~~s~~ 1 ~~to 6~~, wherein the pharmaceutical formulation comprises a pH-adjusting agent.

~~8~~3. The dry pharmaceutical formulation of claim ~~7~~2, wherein the pH-adjusting agent is selected from the group consisting of Tris, sodium hydroxide, potassium hydroxide, lysine and mixtures thereof.

~~9~~4. The dry pharmaceutical formulation of claim~~s 7~~ 2 or ~~8~~3, wherein the pH-adjusting agent is Tris.

~~10~~5. The dry pharmaceutical formulation of ~~any one of~~ claim~~s~~ 1 ~~to 6~~, wherein the pharmaceutical formulation comprises a mixture of one or more acid and base pH-adjusting agents.

~~11~~6. The dry pharmaceutical formulation of any one of claims 1 to ~~9~~4, wherein the pharmaceutical formulation comprises a CNP conjugate, succinic acid, trehalose and Tris.

~~12~~7. The dry pharmaceutical formulation of any one of claims 1 to ~~11~~6, wherein the CNP moiety has the sequence of SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 or SEQ ID NO:30.

~~13~~8. The dry pharmaceutical formulation of any one of claims 1 to ~~12~~7, wherein the CNP moiety has the sequence of SEQ ID NO:24.

~~14~~9. The dry pharmaceutical formulation of any one of claims 1 to ~~13~~8, wherein the polymeric moiety comprises a polymer selected from the group consisting of ~~2 methacryloyl oxyethyl phosphoyl cholins,~~ poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates),

poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

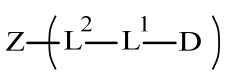
~~15~~10. The dry pharmaceutical formulation of any one of claims 1 to ~~14~~9, wherein the formulation comprises based on the total weight of the dry pharmaceutical formulation:

CNP conjugate	1.3 - 45.4 % (w/w)
succinic acid	0.2 - 3.2 % (w/w)
trehalose dihydrate	52.6 - 98.4 % (w/w)
Tris	0.1 - 5.6 % (w/w).

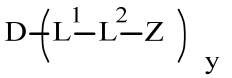
~~16~~11. The dry pharmaceutical formulation of any one of claims 1 to ~~15~~10, wherein the formulation comprises based on the total weight of the dry pharmaceutical formulation:

CNP conjugate	1.3 - 38.7 % (w/w)
succinic acid	0.2 - 3.2 % (w/w)
trehalose dihydrate	52.6 - 98.4 % (w/w)
Tris	0.1 - 5.6 % (w/w).

~~17~~12. The dry pharmaceutical formulation of any one of claims 1 to ~~16~~11, wherein the CNP conjugate is of formula (Ia) or (Ib):



(Ia),



(Ib),

wherein

-D is ~~a~~ the CNP moiety;

-L^1- is a reversible linker moiety;

-L^2- is a single chemical bond or a spacer moiety;

-Z is ~~a~~ the polymeric moiety;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16; and

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5.

~~18~~13. The dry pharmaceutical formulation of claim ~~17~~12, wherein x of formula (Ia) is an integer selected from the group consisting of 1, 2, 3, 4, 6 and 8.

~~19~~14. The dry pharmaceutical formulation of claim ~~17~~12, wherein y of formula (Ib) is an integer selected from the group consisting of 2, 3, 4 and 5.

~~20~~15. The dry pharmaceutical formulation of claim ~~17~~ 12 or ~~18~~13, wherein the CNP conjugate is of formula (Ia) and x is 1.

~~21~~16. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~20~~15, wherein -L^1- is connected to -D through an amide linkage.

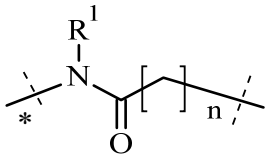
~~22~~17. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~21~~16, wherein the linkage between -Z and -L^2- is a stable linkage.

~~23~~18. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~22~~17, wherein -L^2- is a spacer moiety.

~~24~~19. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~23~~18, wherein -L^2- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

~~25~~20. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~24~~19, wherein -L^2- has a chain length of 1 to 20 atoms.

~~26~~21. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~25~~20, wherein -L^2- is of formula (i):



(i),

wherein

the dashed line marked with the asterisk indicates attachment to -L^1-;

the unmarked dashed line indicates attachment to -Z;

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

n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and

wherein the moiety of formula (i) is optionally further substituted.

~~27~~22. The dry pharmaceutical formulation of claim ~~26~~21, wherein n of formula (i) is selected from the group consisting of 3, 4, 5, 6, 7, 8 and 9.

~~28~~23. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~27~~22, wherein -Z has a molecular weight ranging from 5 to 200 kDa.

~~29~~24. The dry pharmaceutical formulation of any one of claims ~~17~~ 12 to ~~28~~23, wherein -Z comprises a polymer selected from the group consisting of ~~2-methacryloyl-oxyethyl phosphoyl cholins,~~ poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids),

poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

~~30. A method of manufacturing the dry pharmaceutical formulation of any one of claims 1 to 29, wherein the method comprises the steps of~~

~~(i) admixing the CNP conjugate with at least a buffering agent and a bulking agent;~~

~~(ii) adjusting the pH of the admixture of step (i);~~

~~(iii) optionally, filtering the admixture from step (ii);~~

~~(iv) transferring amounts of the admixture from step (ii) or (iii) equivalent to the desired number of dosages into a container;~~

~~(v) drying the admixture;~~

~~(vi) sealing the container; and~~

~~wherein the order of steps (ii) and (iii) may optionally be reversed.~~

~~31. A method of reconstituting the dry pharmaceutical formulation of any one of claims 1 to 29, wherein the method comprises the step of~~

~~(a) contacting the dry pharmaceutical formulation of any one of claims 1 to 29, with a reconstitution solution.~~

~~32. A reconstituted pharmaceutical formulation obtainable from the method of reconstituting of claim 31.~~

~~33. Use of the dry pharmaceutical formulation of any one of claims 1 to 29 or the reconstituted pharmaceutical formulation of claim 32 for the manufacture of a medicament for the treatment of a disease selected from the group consisting of bone-related disorders such as skeletal dysplasias; cancer; autoimmune diseases; fibrotic diseases; inflammatory diseases; central nervous system diseases such as neurodegenerative diseases; infectious diseases; lung diseases; heart and vascular diseases; metabolic diseases and ophthalmic diseases.~~

~~34. The use of claim 33, wherein the disease is achondroplasia.~~