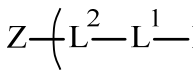
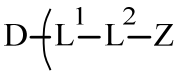
Claims

1. The use of a pharmaceutical composition comprising a water-soluble controlled-release PTH compound in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the water-soluble controlled-release PTH compound has a total mass of at least 20 kDa and from the water-soluble controlled-release PTH compound at least one PTH molecule is released with a release half-life of at least 12 hours, wherein the PTH compound is to be administered to a non-human primate via subcutaneous administration and a time period between two consecutive subcutaneous administrations is at least 24 hours, wherein after subcutaneous administration the pharmacokinetic profile of the PTH compound exhibits a peak to trough ratio of less than 4 within one injection interval of at least 24 hours, wherein the peak to trough ratio is the ratio of the highest plasma concentration to the lowest plasma concentration of released PTH within the time period between the two consecutive administrations to the non-human primate at steady state and wherein the water-soluble controlled-release PTH compound is a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt thereof



(Ia)



(Ib),

wherein

-D is a PTH moiety and has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, 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, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID

NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120 and SEQ ID NO:121;

-L^1- is a reversible prodrug linker moiety connected to the PTH moiety -D through a functional group of PTH;

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

-Z is a PEG-based polymer having a molecular weight of about 40 kDa;

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 or 16; and

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

2. The use of claim 1, wherein the at least one PTH molecule has a sequence selected from the group consisting of SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114 and SEQ ID NO:115.

3. The use of claim 1 or 2, wherein the at least one PTH molecule has the sequence of SEQ ID NO:51.

4. The use of any one of claims 1 to 3, wherein the time period between the two consecutive subcutaneous administrations is 24 hours.

5. The use of any one of claims 1 to 3, wherein the time period between the two consecutive subcutaneous administrations is one week.

6. The use of any one of claims 1 to 5, wherein the subcutaneous administration is via subcutaneous injection.

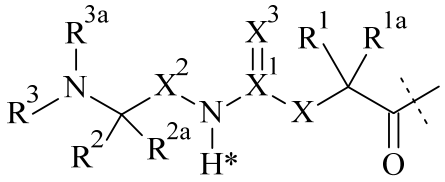
7. The use of any one of claims 1 to 6, wherein the subcutaneous administration occurs with a pen device.

8. The use of any one of claims 1 to 7, wherein the peak to trough ratio is less than 3.

9. The use of any one of claims 1 to 8, wherein the peak to trough ratio is less than 2.6.

10. The use of any one of claims 1 to 9, wherein the non-human primate is a cynomolgus monkey.

11. The use of any one of claims 1 to 10, wherein -L^1- is of formula (II):



(II)

,

wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of -D;

-X- is selected from the group consisting of -C(R^4R^{4a})-; -N(R^4)-; -O-; -C(R^4R^{4a})-C(R^5R^{5a})-; -C(R^5R^{5a})-C(R^4R^{4a})-; -C(R^4R^{4a})-N(R^6)-; -N(R^6)-C(R^4R^{4a})-; -C(R^4R^{4a})-O-; -O-C(R^4R^{4a})-; and -C(R^7R^{7a})-;

X^1 is selected from the group consisting of C; and S(O);

-X^2- is selected from the group consisting of -C(R^8R^{8a})-; and -C(R^8R^{8a})-C(R^9R^{9a})-;

=X^3 is selected from the group consisting of =O; =S; and =N-CN;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^6, -R^8, -R^{8a}, -R^9, and -R^{9a} are independently selected from the group consisting of -H; and C_{1-6} alkyl;

-R^3, and -R^{3a} are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of -R^3, -R^{3a} or both are other than -H they are connected to N to which they are attached through an sp^3-hybridized carbon atom;

-R^7 is selected from the group consisting of -$N(R^{10}R^{10a})$; and -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a}, and -R^{11} are independently of each other selected from the group consisting of -H; and C_{1-6} alkyl;

optionally, one or more of the pairs -R^{1a}/-R^{4a}, -R^{1a}/-R^{5a}, -R^{1a}/-R^{7a}, -R^{4a}/-R^{5a}, and -R^{8a}/-R^{9a} form a chemical bond;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^4/-R^{4a}, -R^5/-R^{5a}, -R^8/-R^{8a}, and -R^9/-R^{9a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9, and -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

optionally, R^3/R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by -L^2-Z or a substituent.

12. The use of any one of claims 1 to 11, wherein -L^2- is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -$C(O)N(R^{y1})$-, -$S(O)_2N(R^{y1})$-, -$S(O)N(R^{y1})$-, -$S(O)_2$-, -S(O)-, -$N(R^{y1})S(O)_2N(R^{y1a})$-, -S-, -$N(R^{y1})$-, -$OC(OR^{y1})(R^{y1a})$-, -$N(R^{y1})C(O)N(R^{y1a})$-, -$OC(O)N(R^{y1})$-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, 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)-, -$C(O)N(R^{y3})$-, -$S(O)_2N(R^{y3})$-, -$S(O)N(R^{y3})$-, -$S(O)_2$-,-S(O)-, -$N(R^{y3})S(O)_2N(R^{y3a})$-, -S-, -$N(R^{y3})$-, -$OC(OR^{y3})(R^{y3a})$-, -$N(R^{y3})C(O)N(R^{y3a})$-, and -$OC(O)N(R^{y3})$-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, 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)-, -$C(O)N(R^{y4})$-, -$S(O)_2N(R^{y4})$-, -$S(O)N(R^{y4})$-, -$S(O)_2$-, -S(O)-,

-N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

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^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), 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

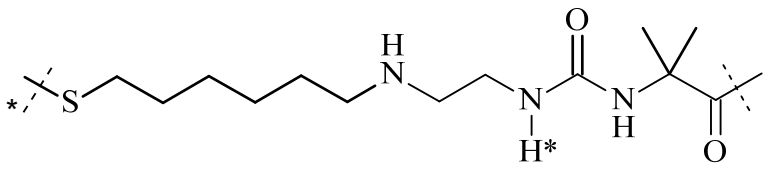
each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently selected from the group consisting of -H, and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

13. The use of any one of claims 1 to 12, wherein -Z is a branched PEG-based polymer.

14. The use of any one of claims 1 to 13, wherein the pharmaceutical composition has a pH ranging from and including pH 3 to pH 8.

15. The use of any one of claims 1 to 14, wherein the pharmaceutical composition has a pH ranging from and including pH 4 to pH 5.

16. The use of any one of claims 1 to 15, wherein the PTH compound is of formula (IIf-i):

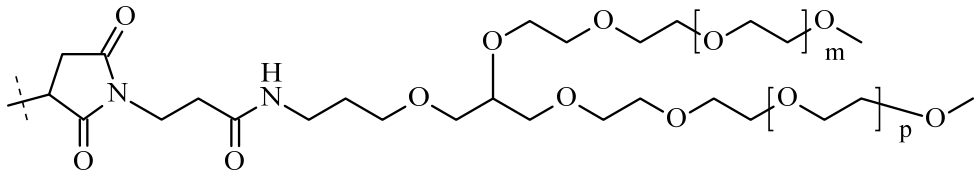


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to a moiety



wherein

m and p are independently an integer ranging from and including 400 to 500.

17. The use of claim 16, wherein m and p are about 450.