Endocrinol Metab 91(8):2926-2930). However, there remains a need for alternative GH therapeutics, dosages, and treatment regimens.

VRS-317 is an investigational long-acting rhGH in development for long-term replacement therapy for adults (including adults who experienced a growth hormone-related disorder as children) with GHD. VRS-317 was designed to achieve once-monthly dosing with the anticipation that a reduced frequency of administration (12 versus up to 365 injections per year) would increase treatment adherence and thereby improve overall treatment outcomes. VRS-317 is a novel rhGH fusion protein that was designed to minimize receptor mediated clearance through a reduction in receptor binding achieved without mutations to rhGH by genetically fusing extended recombinant polypeptide (XTEN) amino acid sequences to the N- and C-termini of the native hGH sequence (Cleland et al. 2012, Journal of Pharmaceutical Sciences. 101(8):2744-2754, Epub 2012 Jun 7). Functionally, the XTEN domains increase the hydrodynamic radius and reduce binding affinity to the GH receptor (GHR), *in vitro*. Despite reduced binding affinity, durable pharmacodynamics response are seen, *in vivo*, possibly relating to reduced rates of receptor mediated clearance of VRS-317 (Cleland et al. 2012 *supra*). VRS-317 was evaluated for safety, tolerability and efficacy in 50 adults with GHD in a 60-day, double-blind, randomized, placebo (PBO)-controlled, single ascending dose escalation studying VRS-317/kg (ClinicalTrials.gov NCT01359488).

SUMMARY OF THE INVENTION

The present invention concerns an improved therapeutic regimen for growth hormone deficiency ("GHD") therapy. In particular, the invention concerns methods for bolus dose administration of compositions of fusion proteins comprising human growth hormone fused to one or more extended recombinant polypeptides (XTEN) (the fusion protein hereinafter referred to as "hGH-XTEN"). Accordingly, in one aspect, the present invention concerns a method of treating human GHD with an hGH-XTEN fusion protein.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for treating human growth hormone deficiency (GHD), wherein the hGH-XTEN fusion protein is

prepared for administering to a human patient with GHD as a therapeutically effective bodyweight adjusted bolus dose between about 0.05 mg/kg and about 3.0 mg/kg.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for treating human growth hormone deficiency (GHD), wherein the hGH-XTEN fusion protein is prepared for administering to a human patient with GHD as a therapeutically effective bodyweight adjusted bolus dose of the hGH-XTEN fusion protein equivalent to less than an hGH/kg/day dosage between about 2 µg hGH/kg/day and about 20 µg hGH/kg/day.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD as a therapeutically effective bodyweight adjusted bolus dose that is effective to maintain the patient's serum IGF-I standard deviation score (SDS) between about -2.0 and about 2.0 for at least 7 days after administration of the bolus dose.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD as a therapeutically effective bodyweight adjusted bolus dose that is effective to maintain a plasma concentration of said fusion protein in the patient at more than about 10 ng/mL for a period of at least 10 days after administration of the bolus dose.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD as a therapeutically effective bodyweight adjusted bolus dose that is effective in increasing the patient's IGF-

I SDS by at least 0.5 or at least 1.0 above the subject's baseline IGF-I SDS in the absence of a clinically significant level of side-effects selected from the group consisting of headache, arthralgia, myalgia, edema, nausea, and muscle fatigue after administration of the bolus dose.

In one aspect, there is provided use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for increasing the efficacy of human growth hormone (hGH) therapy in a human patient with growth hormone deficiency (GHD), wherein dosage of the medicament is based on:

(a) monitoring the IGF-I standard deviation score (SDS) in a plasma or serum sample obtained from the patient during an initial dosage period of administration of an initial dose of human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1; and

(b) determining a subsequent dose of hGH-XTEN fusion protein administered over a subsequent dosage period based on the IGF-I SDS observed during the initial dosage period, wherein the subsequent dose improves the efficacy of the treatment during the subsequent dosage period.

In one aspect, the present invention provides a method of a method of treating human growth hormone deficiency (GHD) in a human patient with an hGH-XTEN fusion protein as a bolus dose. In one embodiment, the method comprises administering to a human patient with GHD an hGH-XTEN fusion protein comprising (i) an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1; or (ii) the amino acid sequence of SEQ ID NO:1. In another embodiment, the hGH-XTEN fusion protein is administered as a therapeutically effective bodyweight adjusted bolus dose. In one

CLAIMS

WHAT IS CLAIMED IS:

1. ~~A method~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 ~~of~~ in the manufacture of a medicament for treating human growth hormone deficiency (GHD), ~~comprising~~ wherein the hGH-XTEN fusion protein is prepared for administering to a human patient with GHD ~~a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1,~~ as a therapeutically effective bodyweight adjusted bolus dose between about 0.05 mg/kg and about 3.0 mg/kg.

2. The ~~method~~ use of claim 1, wherein the bolus dose is to be administered every week, every two weeks, every three weeks, or monthly.

3. The ~~method~~ use of claim 2, wherein the administration of the bolus dose is monthly.

4. The ~~method~~ use of any one of claims 1 to 3, wherein the bolus dose of hGH-XTEN fusion protein is between about 0.05 mg/kg and about 0.8 mg/kg or between about 0.8 mg/kg and about 1.2 mg/kg.

5. The ~~method~~ use of any one of claims 1 to 3, wherein the bolus dose is to be administered subcutaneously.

6. The ~~method~~ use of any one of claims 1 to 3, wherein the human patient has a serum IGF-I standard deviation score (SDS) between about -2.0 and about 2.0 following administration.

7. The ~~method~~ use of claim 6, wherein the IGF-I SDS is selected from the group consisting of greater than about -2.0, greater than about -1.5, greater than about -1.0, greater than about -0.5, greater than about 0, greater than about 0.5, greater than about 1.0, and greater than about 1.5.

8. The ~~method~~ use of claim 6, wherein the human patient exhibits said serum IGF-I SDS following administration of the bolus dose, wherein the administration is weekly, every two weeks, every three weeks, or monthly.

9. The ~~method~~ use of any one of claims 1 to 3, wherein administration of the bolus dose results in a normalization of IGF-I SDS in the human patient for at least about 7 days, at least about 10 days, at least about 14 days, at least about 16 days, or at least about 21 days.

10. The ~~method~~ use of any one of claims 1 to 3, wherein the bolus dose is selected from the group consisting of about 0.05 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.4 mg/kg, about 0.8 mg/kg, about 1.0 mg/kg, about 1.2 mg/kg, about 1.4 mg/kg, about 1.6 mg/kg, about 1.8 mg/kg, about 2.0 mg/kg, about 2.2 mg/kg, about 2.4 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, and about 3.0 mg/kg.

11. The ~~method~~ use of any one of claims 1 to 3, wherein the hGH-XTEN fusion protein comprises the amino acid sequence of SEQ ID NO:1.

12. ~~A method~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1~~of~~ in the manufacture of a medicament for treating human growth hormone deficiency (GHD), ~~comprising~~ wherein the hGH-XTEN fusion protein is prepared for administering to a human patient with GHD ~~a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1,~~ as a therapeutically effective bodyweight adjusted bolus dose of the hGH-XTEN fusion protein equivalent to less than an hGH/kg/day dosage between about 2 µg hGH/kg/day and about 20 µg hGH/kg/day.

13. The ~~method~~ use of claim 12, wherein the bolus dose is to be administered every week, every two weeks, every three weeks, or monthly.

14. The ~~method~~ use of claim 12, wherein the administration of the bolus dose is monthly.

15. The ~~method~~ use of any one of claims 12 to 14, wherein the hGH/kg/day dosage is over about 30 days.

16. The ~~method~~ use of any one of claims 12 to 14, wherein the bolus dose is to be administered subcutaneously.

17. The ~~method~~ use of any one of claims 12 to 14, wherein the human patient has a serum IGF-I standard deviation score (SDS) between about -2.0 and about 2.0 following administration.

18. The ~~method~~ use of claim 17, wherein the IGF-I SDS is selected from the group consisting of greater than about -2.0, greater than about -1.5, greater than about -1.0, greater than about -0.5, greater than about 0, greater than about 0.5, greater than about 1.0, and greater than about 1.5.

19. The ~~method~~ use of claim 17, wherein the human patient exhibits said serum IGF-I SDS following administration of the bolus dose, wherein the administration is weekly, every two weeks, every three weeks, or monthly.

20. The ~~method~~ use of any one of claims 12 to 14, wherein the bolus dose is equivalent to less than an hGH/kg/day dosage selected from the group consisting of about 2 µg hGH/kg/day, about 4 µg hGH/kg/day, about 6 µg hGH/kg/day, about 8 µg hGH/kg/day, about 10 µg hGH/kg/day, about 12 µg hGH/kg/day, about 14 µg hGH/kg/day, about 16 µg hGH/kg/day, about 18 µg hGH/kg/day, about 18.6 µg hGH/kg/day, and about 20 µg hGH/kg/day.

21. The ~~method~~ use of any one of claims 12 to 14, wherein the hGH-XTEN fusion protein comprises the amino acid sequence of SEQ ID NO:1.

22. ~~A method~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1~~of~~ in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, ~~comprising~~ wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD ~~a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1,~~ as a therapeutically effective bodyweight adjusted bolus dose that is effective to maintain the patient's serum IGF-I standard deviation score (SDS) between about -2.0 and about 2.0 for at least 7 days after administration of the bolus dose.

23. The ~~method~~ use of claim 22, wherein the bolus dose is between about 0.05 mg/kg and about 0.8 mg/kg, between about 0.8 mg/kg and about 1.2 mg/kg, or between about 0.05 mg/kg and about 3.0 mg/kg.

24. The ~~method~~ use of claim 22 or 23, wherein said bolus dose is effective to maintain the patient's serum IGF-I SDS between about -2.0 and about 2.0 for at least 20 days after administration of the bolus dose.

25. ~~A method~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1~~of~~ in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, ~~comprising~~ wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD ~~a human growth hormone-XTEN (hGH-~~

~~XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1,~~ as a therapeutically effective bodyweight adjusted bolus dose that is effective to maintain a plasma concentration of said fusion protein in the patient at more than about 10 ng/mL for a period of at least 10 days after administration of the bolus dose.

26. The ~~method~~ use of claim 25, wherein the bolus dose is between about 0.05 mg/kg and about 0.8 mg/kg, between about 0.8 mg/kg and about 1.2 mg/kg, or between about 0.05 mg/kg and about 3.0 mg/kg.

27. The ~~method~~ use of claim 25 or 26, wherein said bolus dose is effective to maintain a plasma concentration of said fusion protein in the patient at more than about 10 ng/mL for a period of at least about 14 days, at least 20 days, at least about 28 days, or at least about 30 days after administration of the bolus dose.

28. The ~~method~~ use of claim 25 or 26, wherein said bolus dose is effective to maintain a plasma concentration of said fusion protein in the patient at more than about 10 ng/mL for a period of at least 20 days or at least about 30 days after administration of the bolus dose.

29. The ~~method~~ use of claim 25 or 26, wherein said bolus dose is effective to maintain a plasma concentration of said fusion protein in the patient at more than about 100 ng/mL for a period of at least 10 days after administration of the bolus dose.

30. ~~A method~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1~~of~~ in the manufacture of a medicament for treating human growth hormone deficiency (GHD) in a human patient, ~~comprising~~ wherein the hGH-XTEN fusion protein is prepared for administering to the patient with GHD ~~a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1,~~ as a therapeutically effective bodyweight adjusted bolus dose that is effective in increasing the patient's IGF-I SDS by at least 0.5 or at least 1.0 above the subject's baseline IGF-I SDS in the absence of a clinically significant level of side-effects selected from the group consisting of headache, arthralgia, myalgia, edema, nausea, and muscle fatigue after administration of the bolus dose.

31. The ~~method~~ use of any one of claims 22, 25, and 30, wherein said bolus dose is to be administered subcutaneously.

32. The ~~method~~ use of any one of claims 22, 25, and 30, wherein the hGH-XTEN fusion protein comprises the amino acid sequence of SEQ ID NO:1.

33. The ~~method~~ use of any one of claims 1, 12, 22, 25, and 30, wherein the human patient has a clinically significant reduction in at least one parameter selected from serum cholesterol, serum triglycerides, and serum low-density lipoprotein (LDL) after administration of the bolus dose, wherein the administration is selected from the group consisting of weekly, every two weeks, every three weeks, and monthly.

34. A bolus dose of an hGH-XTEN fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1, wherein the bolus dose is a therapeutically effective bodyweight adjusted bolus dose comprising between about 0.05 mg/kg and about 3.0 mg/kg of hGH-XTEN fusion protein.

35. The bolus dose of claim 34 for use in treating human growth hormone deficiency (GHD) in a subject in need.

36. The bolus dose of claims 34 or 35, wherein the hGH-XTEN fusion protein comprises the amino acid sequence of SEQ ID NO:1.

37. The bolus dose of claim 34 or 35, which is formulated for subcutaneous administration.

~~38. An hGH-XTEN fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 for use in a method for the treatment of human growth hormone deficiency (GHD) in a human patient, wherein the method comprises administering a therapeutically effective bodyweight adjusted bolus dose of the hGH-XTEN fusion protein at a dose between about 0.05 mg/kg and about 3.0 mg/kg.~~

~~39. Use of an hGH-XTEN fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for the treatment of GHD, wherein the hGH-XTEN fusion protein is administered to a human patient as a therapeutically effective bodyweight adjusted bolus dose of the hGH-XTEN fusion protein at a dose between about 0.05 mg/kg and about 3.0 mg/kg.~~

~~40. The hGH-XTEN fusion protein of claim 38 or the use of claim 39, wherein the bolus dose is administered every week, every two weeks, every three weeks, or monthly.~~

~~41. The hGH-XTEN fusion protein of claim 38 or the use of claim 39, wherein the hGH-XTEN fusion protein comprises the amino acid sequence of SEQ ID NO:1.~~

~~42. The hGH-XTEN fusion protein of claim 38 or the use of claim 39, wherein the bolus dose is administered subcutaneously.~~

~~43. The hGH-XTEN fusion protein of claim 38 or the use of claim 39, wherein the human patient has a serum IGF-I standard deviation score (SDS) between about -2.0 and about 2.0 following administration of the bolus dose.~~

~~44. The hGH-XTEN fusion protein or use of claim 43, wherein the IGF-I SDS is selected from the group consisting of greater than about -2.0, greater than about -1.5, greater than about -1.0, greater than about -0.5, greater than about 0, greater than about 0.5, greater than about 1.0, and greater than about 1.5.~~

~~45. The hGH-XTEN fusion protein or use of claim 43, wherein the administration is weekly, every two weeks, every three weeks, or monthly.~~

~~46. The hGH-XTEN fusion protein of claim 38 or the use of claim 39, wherein the human patient has a clinically significant reduction in at least one parameter selected from serum cholesterol, serum triglycerides, and serum LDL after administration of the bolus dose, wherein the administration is weekly, every two weeks, every three weeks, or monthly.~~

3847. ~~A method of~~ Use of a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1 in the manufacture of a medicament for increasing the efficacy of human growth hormone (hGH) therapy in a human patient with growth hormone deficiency (GHD), ~~comprising~~wherein dosage of the medicament is based on:

(a) monitoring the IGF-I standard deviation score (SDS) in a plasma or serum sample obtained from the patient during an initial dosage period of administration of an initial dose of human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1; and

(b) determining a subsequent dose of hGH-XTEN fusion protein administered over a subsequent dosage period based on the IGF-I SDS observed during the initial dosage period,

wherein the subsequent dose improves the efficacy of the treatment during the subsequent dosage period.

3948. A kit comprising

(i) a container which holds a pharmaceutical composition comprising a human growth hormone-XTEN (hGH-XTEN) fusion protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO:1, and

(ii) a package insert associated with said container, wherein the package insert indicates that said composition is for the treatment of growth hormone deficiency by administration of an initial dose of the hGH-XTEN fusion protein between about 0.05 mg/kg and about 3.0 mg/kg and a plurality of subsequent doses of the hGH-XTEN fusion protein between about 0.05 mg/kg and about 3.0 mg/kg, wherein the doses are administered every week, every two weeks, every three weeks, or monthly.

40. The use of any one of claims 1, 12, 22, 25, 30, and 38 wherein the human patient is an adult.

41. The use of claim 40, wherein the GHD is adult growth hormone deficiency (AGHD).

42. The use of claim 41, wherein AGHD is a continuation of childhood-onset GHD.

43. The use of claim 42, wherein the childhood-onset GHD is selected from Turner's Syndrome, Prader-Willi Syndrome, idiopathic short stature, and intrauterine growth retardation.

44. The use of any one of claims 1, 12, 22, 25, 30 and 38, wherein the hGH-XTEN fusion protein comprises an amino acid sequence having at least 95% identity to SEQ ID NO:1.

45. The use of claim 44, wherein the hGH-XTEN fusion protein comprises an amino acid sequence having at least 98% identity to SEQ ID NO:1.