A Long-Acting Human Growth Hormone With Delayed Clearance (VRS-317): Results of a Double-Blind, Placebo-Controlled, Single Ascending Dose Study in Growth Hormone–Deficient Adults

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Abstract

Background:
Administration of daily recombinant human GH (rhGH) poses a considerable challenge to patient compliance. Reduced dosing frequency may improve treatment adherence and potentially overall treatment outcomes.

Objectives:
This study assessed the safety and tolerability and the potential for achieving IGF-I levels within the target range in adults with GH deficiency after a single dose of the long-acting rhGH analog, VRS-317.

Design:
This was a randomized, double-blind, placebo-controlled, single ascending dose study.

Patients:
Fifty adults with growth hormone deficiency (mean age, 45 years) were studied in 5 treatment groups of 10 subjects each (8 active drug and 2 placebo).

Setting:
The study was conducted in 17 adult endocrinology centers in North America and Europe.

Main Outcome Measures:

Adverse events, laboratory safety assessments, and VRS-317 pharmacokinetics and pharmacodynamics (IGF-I and IGF binding protein-3) were analyzed.

Results:

At 0.80 mg/kg, VRS-317 had a mean terminal elimination half-life of 131 hours. Single VRS-317 doses of 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg (approximately equivalent to daily rhGH doses of 0.3–5.0 μg/kg over 30 d) safely increased the amplitude and duration of IGF-I responses in a dose-dependent manner. After a single 0.80 mg/kg dose, serum IGF-I was maintained in the normal range between −1.5 and 1.5 SD values for a mean of 3 weeks. No unexpected or serious adverse events were observed.

Conclusions:

The elimination half-life for VRS-317 is 30- to 60-fold longer and stimulates more durable IGF-I responses than previously studied rhGH products. Prolonged IGF-I responses do not come at the expense of overexposure to high IGF-I levels. The pharmacokinetics and pharmacodynamics combined with the observed safety profile indicate the potential for safe and effective monthly dosing.

Achievement of treatment goals with recombinant human GH (rhGH) typically requires years of treatment. Maintaining full compliance with daily injections has been difficult for many patients and dose omissions occur frequently (1–4). In children, a lack of compliance with daily rhGH has been associated with significantly diminished growth velocities (5). A long-acting rhGH may reduce dosing frequency, improve compliance, and potentially improve overall treatment outcomes.

The potential benefits of a long-acting human GH (hGH) were recognized and explored more than 30 years ago (6) and a sustained-release rhGH (7–10) was approved for children but later withdrawn from distribution because of difficulties with manufacturing of the product. Since then, studies have been performed with a variety of modified rhGH molecules that may be suitable for weekly administration (11–18), but none has shown duration of action extending beyond 1 week and none has yet received approval from US or European Union regulatory authorities.

VRS-317 is a long-acting rhGH in development for use as long-term replacement therapy in adults and children with growth hormone deficiency (GHD). It is a fusion protein (molecular mass of 119 kDa) produced in Escherichia coli. The pharmacologically active portion is the rhGH domain (22 kDa), and the pharmacologically inactive domains are long chains of natural hydrophilic amino acids, referred to as XTEN (19). The XTEN domain enables extension of the half-life of rhGH by increasing the hydrodynamic size of rhGH and delaying receptor-mediated clearance. Although the in vitro potency of VRS-317 was reduced by approximately 12-fold compared with that of rhGH, the in vivo potency was increased because of the greatly prolonged exposure at the target tissues (20).

In light of previous pharmacokinetic (PK) and pharmacodynamic (PD) studies (10–15, 18) using sustained-release GH preparations, we performed a randomized, double-blind, placebo-controlled, multicenter, single ascending dose study, and we report the results of the safety, tolerability, and PK/PD of VRS-317 in adults with GHD.

Patients and Methods

Subject characteristics

Subjects had GHD as confirmed by a negative response to insulin (peak GH, <5.0 ng/mL), arginine-GHRH (peak GH based on body mass index [BMI]) (21, 22), glucagon (peak GH, <3.0 ng/mL) (23), or at least 3 other pituitary
hormone deficiencies and a low IGF-I for age and sex (21). When GHD was due to a lesion in the sellar region, surveillance magnetic resonance imaging scans showed at least 6 months of stability. Treatments for other pituitary hormone deficiencies were stable for 2 months before study drug administration. Free T₄ was in the normal range for all subjects when VRS-317 was administered. Each subject not receiving daily glucocorticoid treatment had normal responses to a standard-dose (250 μg) ACTH test to rule out secondary adrenal insufficiency. For female patients receiving estrogen, transdermal treatment was used and maintained throughout the study. Serum IGF-I responses to daily rhGH were characterized in all subjects before study drug administration. Key exclusion criteria included the presence of significant concurrent disease (e.g., diabetes), active malignancy, anti-hGH antibodies at screening, pregnancy, or lactation or the use of oral estrogens.

Dose selection

Because in vivo potency was enhanced in monkeys (20), the VRS-317 dose range for the first dose in humans was selected to approximate the daily rhGH doses in the lower half of the typical dosing range for each 30-day interval (i.e., 0.03–0.5 mg rhGH/d or approximately 0.3–5.0 μg/kg/d). The VRS-317 doses selected were 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg administered as a single sc injection.

Study procedures and method of study

All patients provided signed informed consent before any study activity. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki with site-specific regulatory and ethics approval. The trial was performed in 17 endocrine centers under an investigational new drug application to the US Food and Drug Administration, clinical trial applications in Canada and the United Kingdom, and analogous clinical trial submissions in Sweden and Serbia. Initially, all subjects were given daily rhGH for a minimum of 28 days and until 2 successive IGF-I standard deviation scores (SDSs), measured at least 1 week apart, were within the range of −1.5 to 1.5 (+2.0 for men). Subjects were then withdrawn from daily rhGH until their IGF-I SDS decreased by at least 0.75 and had dropped to ≤−1.0. Subjects were then randomized to the treatment cohort enrolling at that time. On day 1, all subjects were admitted to the hospital and received a single sc dose of VRS-317 or placebo with an insulin syringe with a 29-gauge needle. Samples for PK/PD analysis were collected predose and at 0.5, 1.0, 2, 4, 8, 12, 24, 36 and 48 hours. Outpatient visits and additional PK/PD sampling were conducted on days 4, 8, 11, 15, 18, 22, 25, and 30. Glucose and lipid metabolism was assessed predose and on days 8, 15, 22, 30, 44, and 60. Testing for anti–VRS-317 antibodies was conducted predose and on days 30 and 60. Before proceeding to the next dosing level, safety data from at least 8 patients with a minimum of 7 days postdosing data were reviewed to ensure that the prespecified stopping criteria were not met before dose escalation. Adverse events were collected at each visit and graded using Common Terminology Criteria for Adverse Events (CTCAE) (24). Erythema and edema at injection sites were graded using the Draize technique (25).

Laboratory safety assessments were performed before and at selected times after dosing. Tests included standard blood counts, biochemistry analyses, fasting and postprandial glucose levels after a standard meal, hemoglobin A₁c (HbA₁c), and fasting levels of cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.

Definition of patient populations

The safety population consisted of all 50 randomized subjects. The PK/PD population consisted of 48 subjects receiving either VRS-317 or placebo and excluded 2 subjects who received inappropriate doses for their weight (1 subject in the 0.80 mg/kg dose group and 1 subject in placebo group).

Assays

All assays were performed in central laboratories. VRS-317 concentrations were measured in plasma using an ELISA. The assay uses capture and detection antibodies to the XTEN and rhGH domains, respectively, to ensure
A single sc dose resulted in rapid absorption and prolonged serum exposure to VRS-317 (Figure 1). Mean maximal VRS-317 plasma concentrations ($C_{\text{max}}$) were reached at 44 to 82 hours. VRS-317 exposure was directly proportional to dose. There was a general trend for VRS-317 elimination half-life ($t_{1/2}$) to increase with increasing dose. The mean $t_{1/2}$ was 131 hours at the highest dose tested (0.80 mg/kg) (Table 2). In multivariate analyses, the
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AUC₀₋₄ for VRS-317 was highly correlated to dose ($P < .0001$), but no significant age or sex effect was observed in this population.

**Figure 1.**
Time course of mean VRS-317 concentrations in adult subjects with GHD receiving a single sc dose on day 1. Subjects received a single sc dose of either 0.05 (▲), 0.10 (■), 0.20 (□), 0.40 (●) or 0.80 (○) mg/kg VRS-317. ...

**Table 2.**
VRS-317 PK Parameters in GH-Deficient Adults After a Single Subcutaneous Injection

**Pharmacodynamics**

Serum IGF-I concentration was the primary PD marker for this study. The amplitude and duration of IGF-I exposure was directly proportional to the VRS-317 dose (Figure 2A and Table 3). The maxima for mean changes in IGF-I concentrations and IGF-I SDS were similar for the 0.40 and 0.80 mg/kg groups. The similarity may have been caused by the uneven distribution of subject characteristics affecting IGF-I responses to VRS-317. Therefore, an ANCOVA was used to examine the set of all postdose values of IGF-I concentration for dependencies on age, sex, treatment day, VRS-317 dose, treatment by day interaction (as factors), and baseline (predose) IGF-I concentration (as covariate). Dose, day, and dose and treatment × day interaction were all significant ($P < .0001$) as were age ($P = .0034$) and sex ($P = .0224$). Higher doses, male sex, and younger age were all associated with greater IGF-I responses.

**Figure 2.**
A, Mean change in IGF-1 SDS for placebo and 5 VRS-317 dosing groups. Data represent the mean of subjects in a dose group for the differences for each subject between his or her baseline and each subsequent time point and are not the absolute mean IGF-1 ...

**Table 3.**
PD Response Summary of IGF-I to a Single Dose Administration of VRS-317 in the PK/PD Population (n = 48)

The extent and duration to which IGF-I SDS were normalized were also VRS-317 dose dependent. An analysis of subjects having an IGF-I SDS less than −1.5 at the time of dosing indicated that VRS-317 increases IGF-I SDS into the target range of −1.5 to 1.5 in a dose-dependent manner (Figure 2B). IGF-I SDS was normalized for a mean of approximately 3 weeks for the 0.80 mg/kg group. This prolonged duration of normalization did not come at the expense of overexposure to IGF-I. The 40 VRS-317–treated patients had a total of 513 postdose IGF-I SDS determinations and only 8 values (1.6%) in 6 patients were above the normal range (SDS >+2). The individual IGF-I SDSs greater than +2 (ranging from 2.01 to 3.59) were observed only in the 0.40 and 0.80 mg/kg groups and usually occurred within 72 hours after dosing and had normalized by the subsequent sampling time.

IGFBP-3 SD scores were low at baseline (mean, −1.28; SD, 1.82) but increased with VRS-317 dosing. The time course of change in IGFBP-3 was similar to that of IGF-I. Maximal IGFBP-3 responses were generally observed at day 4 or day 8. The changes in IGFBP-3 levels were dose dependent. At day 8, the least square mean changes in IGFBP-3 were 0.05, 0.17, 0.55, 0.80, and 1.41 mg/L (IGFBP-3 SDS $C_{max}$ of −0.6 to 2.6) for the 0.05, 0.10, 0.20, 0.40, and 0.80 mg/kg dosing groups, respectively. In ANCOVA, IGFBP-3 responses were dependent on the VRS-317 dose, day, and baseline value (all $P < .0001$), but no effects of age or sex were observed. At baseline, the IGF-I/IGFBP-3 molar ratio was 0.22 ± 0.05 and did not differ among the different dosing groups ($P = .49$). Mean

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maximal molar ratio values were observed on day 4 and increased with increasing VRS-317 dose (P < .0001). The maximal mean molar ratio for the 0.80 mg/kg group was 0.47 ± 0.11. The maximal molar ratio value for any subject was 0.65.

**Safety results**

Per protocol, safety data from a minimum of 8 patients exposed for a minimum of 7 days were reviewed before patients were enrolled in the next higher dose level. None of the protocol-specified stopping criteria were met; consequently, all 5 planned dosing levels were studied. There were no unexpected adverse events (AEs) related to the study drug.

Nonlaboratory AEs considered to be related to the study drug by investigators were transient and mild (CTCAE grade 1 except for 2 cases of grade 2) and occurred in a minority of subjects (Table 4). Many related events (headache [4], arthralgia [3], myalgia [1], and edema [1]) were of the type typically observed when rhGH therapy is started in adult patients with GHD. The 0.40 and 0.80 mg/kg dosing groups had the greatest number of any related AEs (7 in each group), but no specific event had a clear dose relationship.

![Table 4. Treatment-Emergent Adverse Events Possibly, Probably, or Definitely Related to Study Drug Administration in the Safety Population (n = 50)](image)

Injection site reactions were the most commonly reported drug-related AEs. Injection site erythema was noted in 30% of VRS-317–treated and 10% of placebo-treated subjects. Injection site edema was noted in 10% of VRS-317–treated subjects and 10% of placebo-treated subjects. Injection site pain or tenderness was observed in 15% of VRS-317–treated subjects. Injection site reactions appeared within 24 hours and were mild (Draize I, barely perceptible) and transient. There were no instances of injection site lipoatrophy or hypersensitivity reported throughout 60 days of posttreatment observation.

There were no reported safety events or clinically meaningful changes related to any glucose metabolism parameter. No patient had a glucose result in the diabetic range (fasting glucose ≥126 mg/dL and postprandial glucose ≥200 mg/dL). All mean and individual values for HbA₁c remained within the normal range. No clinically meaningful changes (≥0.2%) were noted in change from baseline HbA₁c vs placebo in any treatment group. One patient each from the 0.10 and 0.20 mg/kg dosing group had worsening of previously elevated levels of serum cholesterol, LDL, and triglycerides as possibly related AEs. However, at the highest VRS-317 dose (0.80 mg/kg), there was a temporal pattern of reduction in cholesterol, LDL, and triglycerides, maximal at day 8 and persisting through day 22. The maximal percent decreases from baseline were 11.3 (P = .0026), 14.6 (P = .014), and 14.5% (P = .19) for cholesterol, LDL, and triglycerides, respectively.

**Antibody assessments**

Nonspecific binding was noted in the anti-hGH antibody assay. As required by the inclusion criteria, no subject had a significant titer (≥1:10) of specific anti-rhGH antibodies at screening, and no subject tested positive at 7 days after daily rhGH withdrawal. A single subcutaneous administration of VRS-317 to adult GHD patients previously treated with daily rhGH resulted in a minority of subjects (4 of 40) generating an anti–VRS-317 antibody response at a low titer (3 of 4 subjects at 1:5 and 1 subject at 1:25). Three of these 4 subjects had nonspecific binding in the anti-hGH antibody assay. Analysis of potential antibody effects on clinical or pharmacological endpoints was precluded by the low number of subjects testing positive for anti–VRS-317; there were no notable differences in IGF-I responses with these 4 subjects.

**Discussion**
VRS-317 is an investigational long-acting rhGH in development for long-term replacement therapy for adults and children with GHD. VRS-317 was designed to achieve once-monthly dosing with the anticipation that a reduced frequency of administration (12 vs up to 365 injections per year) would increase treatment adherence and thereby potentially 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 without mutations to rhGH by genetically fusing XTEN amino acid sequences to the N and C termini of the native hGH sequence (20). Functionally, the XTEN domains increase the hydrodynamic radius and reduce binding affinity to the GH receptor in vitro. Despite reduced binding affinity, durable PD responses are seen in vivo, possibly relating to reduced rates of receptor-mediated clearance of VRS-317 (20). The reduced rate of clearance significantly prolongs serum residence times of VRS-317, resulting in enhanced ligand time on target and potentially increasing the probability of a successful ligand-receptor interaction. The terminal elimination half-life of VRS-317 at the highest dose was 131 hours; this represents a 30- to 60-fold increase over those reported in package inserts for daily rhGH.

The current study was the first in humans for VRS-317 and extends prior knowledge about long-acting rhGH because it represents the most prolonged duration of action of any rhGH analog in the treatment of adults with GHD. All subjects were adults with GHD diagnosed in accordance with current consensus guidelines of The Endocrine Society (21), the American Association of Clinical Endocrinologists (22), and the Growth Hormone Research Society (26). There was a slight preponderance of male subjects (29 men and 21 women), but the numbers of each sex were adequate to test for sex effects on drug distribution and PD effects. Each subject was initially stabilized with daily rhGH injections and to achieve stable IGF-I SDSs within the normal range had been taking 0.2 to 1.0 mg of hGH/d (1.5–10.5 μg/kg/d) (mean, 0.6 mg/d). After discontinuation of daily rhGH, IGF-I SDSs decreased in all subjects with group mean decrements of 1.7 to 2.4 SD. Subjects requiring daily medication that could alter sensitivity to rhGH (e.g., insulin, oral estrogens, and anti-inflammatory doses of glucocorticoids) were excluded from this first dosing study of VRS-317.

Over the VRS-317 dosing range, drug exposure parameters (C_max and AUC) were directly and highly proportional to dose. In general, both the amplitude and duration of exposure increases with increased VRS-317 doses. No sex or age effects were detected in the VRS-317 dose-exposure relationship. VRS-317 was safe and well tolerated at all dose levels, suggesting that greater dose and duration of exposures can be explored in future human studies. The PD (IGF-I and IGFBP-3) responses to VRS-317 were also directly proportional to dose, with amplitude and duration increasing with increased dose. At the highest dose, the mean IGF-I SDS was maintained at greater than −1.5 for approximately 3 weeks. Given the demonstrated proportionality between dose and duration, the duration of IGF-I normalization could be extended by increased VRS-317 doses. Over the dose range assessed in this study, the duration of IGF-I normalization does not come at the expense of overexposure to IGF-I because only 1.6% of IGF-I SDSs were ≥2; moreover, these elevations were transient. There were age and sex effects on IGF-I responses to VRS-317. Women and older subjects had lower IGF-I responses than men and younger subjects. Sex differences for IGF-I induction are well known for daily rhGH and are likely to be due to estrogen effects on the liver affecting IGF-I production (27–30). Similar to the effects of daily rhGH, IGF-I induction by VRS-317 in adults may be lower in women than in men.

VRS-317 was administered at doses from 0.05 to 0.80 mg/kg, approximating daily rhGH doses of 0.3 to 5.0 μg/kg/d over 30 days. Over this range, a single dose of VRS-317 was safe and well tolerated. There were no treatment-emergent serious AEs or suspected unexpected serious adverse reactions. No subject withdrew from the study after dosing; all subjects completed the protocol-specified 60-day safety observation period. Minimal transient erythema at the injection site(s) was the most commonly reported AE. Other events considered as possibly, probably, or definitely related to the study drug were typical of those seen when adult patients with GHD receive replacement therapy. These events were transient and were categorized as mild to moderate. No injection site lipoatrophy was observed. Surveillance for VRS-317 alterations in carbohydrate metabolism included serial measurements of fasting glucose and insulin, postprandial glucose, and HbA1c. No clinically meaningful temporal or dose-related changes were observed in any of these parameters, indicating that the prolonged action and delayed clearance of VRS-317 did not confer any additional risk to overall glycemic safety in these patients. These findings...
are in accordance with previous studies using low doses of daily rhGH (23, 31–34) but in contrast to other studies showing elevated glucose and insulin with decreased insulin sensitivity indices using higher rhGH doses (>0.6 mg/d) (35–37). Although 2 subjects in a lower dose group had increases in previously elevated levels of LDL, total cholesterol, and triglycerides, there was a temporal pattern of decrease in these parameters with the highest VRS-317 dose (0.80 mg/kg). It is thought that rhGH dose and duration effects as well as individual susceptibility will influence glucose, lipid, and insulin responses. Continued surveillance for alterations in lipid and glucose parameters is warranted during subsequent chronic dosing trials (38).

Four of the 40 VRS-317–treated subjects had detectable anti–VRS-317 antibodies appearing at days 30 and/or 60 after VRS-317 dosing. These subjects had received VRS-317 doses of 0.20 mg/kg (1 subject), 0.40 mg/kg (2 subjects), and 0.80 mg/kg (1 subject). Three of these 4 had had nonspecific binding in the anti-rhGH antibody screening assay. Additional testing of adult subjects with GHD who are naive to treatment and testing during repeat dosing will be required to better assess the immunogenicity of VRS-317.

In conclusion, single-dose administration of VRS-317 is safe and well tolerated over the range of doses studied and provides prolonged normalization of IGF-I responses in adults with GHD. The safety and PK/PD profiles indicate that VRS-317 doses may be further increased to prolong IGF-I responses in this population. With monthly VRS-317, IGF-I SDS may be normalized for prolonged periods with minimal risk of exposure to supraphysiological IGF-I levels. Given its delayed clearance, VRS-317 has the potential for monthly dosing in adults with GHD.

### Supplementary Material

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### Acknowledgments

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This study was registered with clinical trial registration number [NCT01359488](www.ClinicalTrials.gov).


### Footnotes

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Abbreviations:

AE. adverse event  
ANCOVA. analysis of covariance  
AUC. area under the curve
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References


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