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Children with Growth Hormone Deficiency Treated with Lonapegsomatropin Demonstrated Sustained Height Improvements for up to 6 Years: enliGHten Trial Final Results

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Keywords
Long-acting growth hormone · Pediatric growth hormone deficiency · Final adult height

Abstract
Introduction: This international, Phase 3, open-label extension trial evaluated the long-term safety and efficacy of once-weekly lonapegsomatropin in children with growth hormone deficiency (GHD). ***Methods:*** Conducted across 63 sites (15 countries), the enliGHten trial enrolled children with GHD who previously participated in a Phase 3 lonapegsomatropin trial (heiGHt or fliGHt). Participants received subcutaneous injections of lonapegsomatropin dosed at 0.24 mg hGH/kg/week. Safety was monitored through adverse events, local tolerability, hormone levels, and metabolic parameters. Efficacy was evaluated through annualized height velocity (AHV), change in height standard deviation score (SDS), and IGF-1 SDS. ***Results:*** Lonapegsomatropin demonstrated sustained efficacy with mean height SDS (−0.39 at year 4, $n = 298$) approaching the mean for children of average stature (height SDS = 0) over time. Eighty-one participants completed treatment for pediatric GHD during the trial, and 48 (59.3%) of these met or exceeded their average parental height SDS at their last visit. For the full population, mean values of weekly average IGF-1 remained within 0–2 SDS throughout the trial. Growth was maintained throughout pubertal development and the dose remained stable throughout the trial. Adverse events were mostly mild or moderate and remained consistent with prior reports of daily somatropin with no evidence of accelerated skeletal maturation or safety signals associated with anti-drug

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antibodies. ***Conclusion:*** Treatment of pediatric GHD with lonapegsomatropin in the enliGHten trial provided robust growth outcomes and maintained a safety profile comparable to that of daily GH in a population with a broad range of pubertal statuses.

Introduction

Growth hormone deficiency (GHD) is a complex endocrine disorder characterized by inadequate secretion of growth hormone from the pituitary gland, resulting in impaired linear growth in children, as well as various physiological and metabolic disturbances in both children and adults [1]. Daily somatropin (recombinant human growth hormone) has been the standard of care for GHD for decades, but registry data and surveys suggest that patients may have poor adherence to daily somatropin, which is associated with suboptimal growth outcomes [2].

Given that adherence to daily injections poses a significant treatment challenge, particularly in the pediatric population for a condition that requires several years of treatment, efforts have been directed toward developing long-acting growth hormone (LAGH) therapies. The goal for LAGH therapies has been less frequent administration while maintaining efficacy and safety comparable to daily somatropin [2].

Lonapegsomatropin (TransCon hGH; SKYTROFA®), a prodrug of somatropin, is administered once weekly and is approved in the USA by the FDA for pediatric patients aged 1 year and older, weighing at least 11.5 kg, and by the European Commission (EC) for children and adolescents aged 3–18 years, for treating growth failure due to GHD [3, 4]. Lonapegsomatropin allows for the sustained release of active, unmodified somatropin with the identical 191 amino acid sequence and size (22 kDa) as endogenous growth hormone [5, 6].

In the pivotal Phase 3 heiGHt trial, lonapegsomatropin demonstrated non-inferiority and superiority in annualized height velocity (AHV) at Week 52 compared with somatropin in treatment-naive children with GHD [6]. Furthermore, the Phase 3 fliGHt trial showed that children previously treated with somatropin could be successfully transitioned to lonapegsomatropin, with continued linear growth and a comparable safety profile to daily somatropin [7]. Following completion of the heiGHt or fliGHt trial, participants were invited to enroll in the enliGHten trial. Previously, 2-year outcomes from the enliGHten trial have been reported [8]. This manuscript presents the final analysis of the Phase 3, open-label, international enliGHten extension trial.

Materials and Methods

Trial Oversight

The trial protocol was approved by the Institutional Review Board of each participating site. Informed consent was obtained from the parent or legal guardian of each participant, and written assent from the participants was required for inclusion in the trial. An independent safety committee provided trial oversight to ensure participant safety and data integrity throughout the trial.

Trial Design

The enliGHten trial (NCT03344458) was a Phase 3 open-label extension trial designed to evaluate the longer-term efficacy and safety of once-weekly lonapegsomatropin in children with GHD from December 2017 to February 2023. The trial was conducted across 63 specialized clinical sites in 15 countries across North America (58.7%), Europe (32.2%), Oceania (4.7%), and the Middle East and North Africa (4.4%). Visits occurred every 13 weeks.

As previously reported, the heiGHt trial (NCT0278 1727) was a 52-week, open-label, active-controlled, pivotal Phase 3 trial evaluating treatment-naive, prepubertal children (males aged 3–12 years; females aged 3–11 years) with GHD. Participants were randomized 2:1 to receive either once-weekly lonapegsomatropin (0.24 mg hGH/kg/week) via vial/syringe or an equivalent weekly dose of daily somatropin via vial/syringe [6]. The fliGHt trial (NCT03305016) was a 26-week, open-label Phase 3 trial evaluating treatment-experienced children (aged 6 months to 17 years; participants <3 years old could be treatment-naive) with GHD who switched from their previous daily somatropin regimen to lonapegsomatropin (0.24 mg hGH/kg/week) via vial/syringe [8].

Trial Participants

Participants who completed the heiGHt [6] or fliGHt [7] trial and met all other eligibility criteria for the enliGHten trial were invited to participate. Eligibility criteria ensured that participants did not have closed epiphyses (defined as bone age >14.0 years for females and >16.0 for males), poorly controlled diabetes mellitus (HbA1c ≥8.0%) or diabetic complications, or other major medical conditions at enliGHten baseline.

Interventions

All participants were assigned to receive lonapegsomatropin at a dose of 0.24 mg hGH/kg/week, the same starting dose used in the parent trials heiGHt or fliGHt. If

the lonapegsomatropin dose had been adjusted during the previous trial the most recent dose was continued at the beginning of the enliGHten trial. Lonapegsomatropin was provided in single-use glass vials and administered with a syringe and needle, available in 12.1 mg hGH/vial or 24.2 mg hGH/vial strengths. An auto-injector developed specifically to deliver once-weekly lonapegsomatropin was made available to participants in the USA. This auto-injector uses dual-chamber cartridges (DCCs) containing lyophilized drug product in one chamber and sterile water for injection in the other. Through a series of steps, the auto-injector automatically reconstitutes the drug for administration. Once available, 163 (93.7%) of the 174 US participants switched to administration using the auto-injector.

Lonapegsomatropin was injected subcutaneously once weekly into the left or right buttock, left or right thigh, or left or right abdomen by the participant or parent/legal guardian/caregiver. To minimize local side effects, it was recommended to rotate the injection sites. Dosing and dose adjustments were made based on a bracketed dosing, choosing among cartridges delivering lonapegsomatropin doses varying in 20% increments. The available cartridges delivered 3, 3.6, 4.3, 5.2, 6.3, 7.6, 9.1, 11, or 13.3 mg hGH. When administered using vials, lonapegsomatropin doses were chosen to match those of the cartridges. Doses could be adjusted at the discretion of the investigator due to symptoms or laboratory results. The protocol-specified target IGF-1 SDS range was 0 to +2.0. Thus, if the average IGF-1 SDS at a visit was <0 or >+2.0, the lonapegsomatropin dose may have been increased or decreased, respectively, by approximately 20% to the dose corresponding to the next higher or lower cartridge dose strength.

Safety Assessments

Safety assessments at each 13-week visit included adverse events (AEs), local tolerability, chemistry and hematology parameters, hormone levels (including thyroid status and morning cortisol), parameters of glucose and lipid metabolism, immunogenicity, fundoscopy, pubertal status, bone age, and vital sign measurements. Bone age X-ray was required to be completed once every 12 months but may have been performed at any time if clinically indicated. Images were sent to an external central reader who assessed the bone age using the Greulich and Pyle method [9].

Efficacy Assessments

Efficacy was evaluated through AHV and the change from baseline in height SDS (calculated using CDC 2000 growth charts) [10].

Pharmacodynamics

Serum IGF-1 measurements were collected in the morning at baseline (Day 1 of the extension trial, the same day as the final visit of the heiGHt or fliGHt trial) and 5 days (±1 day) after dosing at all visits (±2 weeks). Due to differences in sampling at the final visit in the heiGHt or fliGHt trials, the extension trial baseline IGF-1 SDS corresponded to levels at different post-dose time points for each group. For the heiGHt lonapegsomatropin group, the enliGHten baseline IGF-1 was sampled approximately 7 days post-lonapegsomatropin dose, corresponding to a trough IGF-1 level. For the heiGHt somatropin group, the enliGHten baseline IGF-1 SDS was sampled after the last somatropin dose, corresponding to a peak IGF-1 SDS level. For the fliGHt lonapegsomatropin group, the enliGHten baseline was sampled approximately 5 days post-lonapegsomatropin dose, corresponding to the weekly average IGF-1 SDS. IGF-1 SDS was calculated based on age- and sex-adjusted reference levels and as previously reported [6, 11].

Statistical Analyses

All analyses were performed on the full analysis set (FAS), which included all participants who signed informed consent for the extension trial and received at least one dose of lonapegsomatropin. A subset of participants was designated as "treatment completers," defined as those who, according to the investigator's judgment, had achieved near adult height and treatment objectives for pediatric GHD [12]. Bone age assessment of the left hand and wrist was included in the consideration (e.g., bone age >14.0 years for females and >16.0 years for males). In general, the baseline for the FAS in the enliGHten trial was the last non-missing assessment collected in heiGHt or fliGHt before the first lonapegsomatropin dose in enliGHten.

Immunogenicity analyses evaluated antibody status during lonapegsomatropin treatment across heiGHt, fliGHt, and enliGHten, with baseline reflecting the last assessment before the first dose of lonapegsomatropin across the three trials. Post hoc analyses combining data from the heiGHt and fliGHt trials with this extension trial were performed. Baseline was the last non-missing assessment collected before the first lonapegsomatropin treatment in heiGHt, fliGHt, or enliGHten. Mean (SD) AHV was analyzed by participant age and year of lonapegsomatropin treatment (in completed years) for female and male patients. Annual assessments on lonapegsomatropin treatment through Week 312 across the heiGHt, fliGHt, and enliGHten trials were included in the analysis. Post hoc analyses by Tanner stage was

Table 1. Full analysis set: demographics and key data at baseline and the last visit

Baseline demographics in enliGHten	Variable	Total (*N* = 298)
Age, years	Mean (SD) Min, max	10.3 (3.4) 1.7, 17.8
Sex, *n* (%)	Male	235 (78.9)
Height SDS	Mean (SD)	−1.6 (0.88)
IGF-1 SDS	Mean (SD)	1.0 (1.30)
Tanner stage, *n* (%)	Stage I Stage II Stage III Stage IV Stage V	214 (71.8) 40 (13.4) 25 (8.4) 16 (5.4) 3 (1.0)
Key data at the last visit in enliGHten	**Variable**	**Total (*N* = 298)**
Age, years	Mean (SD) Min, max Male, mean (SD) Female, mean (SD)	13.8 (3.0) 5.5, 18.6 14.0 (3.0) 12.6 (2.7)
Tanner stage, *n* (%)	Stage I Stage II Stage III Stage IV Stage V	89 (29.9) 32 (10.7) 28 (9.4) 63 (21.1) 86 (28.9)
Duration of lonapegsomatropin treatment during the enliGHten trial, years	Mean (SD) Min, max	3.5 (1.0) 0.1, 5.0
Duration of total lonapegsomatropin treatment (heiGHt or fliGHt plus enliGHten), years	Mean (SD) Median Min, max	4.1 (1.1) 4.3 0.5, 6.0

conducted for IGF-1 SDS, lonapegsomatropin dose, and AHV. A mixed model for repeated measures (MMRM) was used to estimate these outcomes at each Tanner stage. Details of each model are described in the footnotes of the respective figures.

Results

Outcomes, Demographics, and Exposure (Full Analysis Set)

Participant characteristics at the start of the enliGHten trial and at the participants' last visit are summarized for the full analysis set (*N* = 298) in Table 1. Approximately 80% of the participants were male. At the start of the enliGHten trial, participants had mean (SD) age 10.3 (3.4) years, ranging from 1.7 to 17.8 years. By completion of the enliGHten trial, the mean (SD) age was 13.8 (3.0) years, ranging from 5.5 to 18.6 years, with half in Tanner Stage IV (21.1%) or Stage V (28.9%). Mean (SD) peak stimulated GH prior to GH therapy was 5.8 (2.7) ng/mL, with 35.9% of participants having a peak stimulated GH of ≤5 ng/mL.

Across the heiGHt, fliGHt, and enliGHten trials, total lonapegsomatropin treatment duration was up to 6.0 years, with a median of 4.3 years (Table 1). Participants from the fliGHt trial had a median daily somatropin treatment duration of 1.1 (0.7) years (range, 0.3–4.0 years) prior to treatment with lonapegsomatropin [7]. In longitudinal data displayed for the full analysis set through Week 208, the decrease in number of participants over time is mainly attributable to participants who, according to the protocol criteria, had reached final or near final height and completion of GH treatment was recommended. Additional reasons for assessments not collected at different time points are shown in online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000545064).

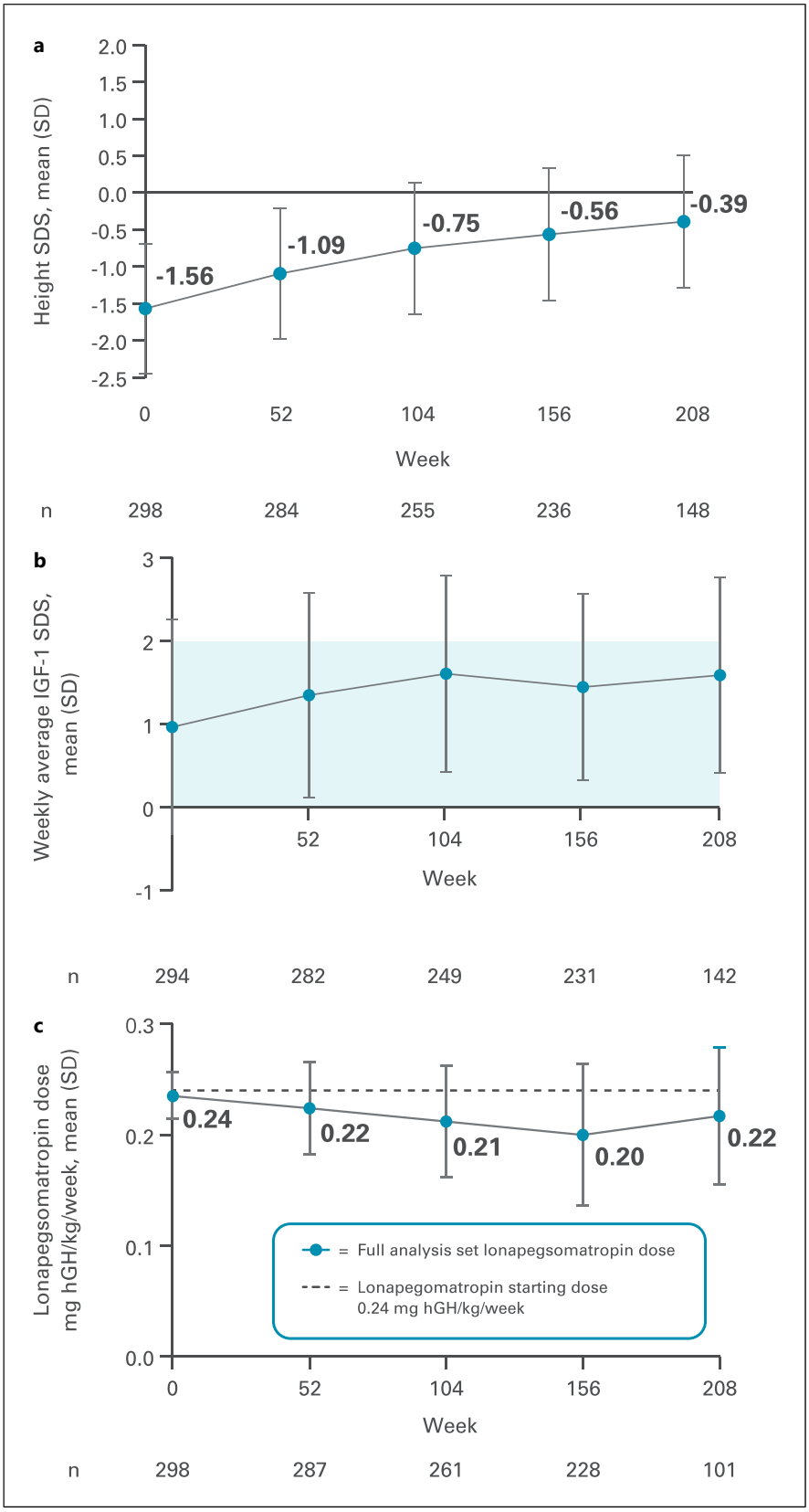


Fig. 1. Longitudinal assessments over 4 years of the enliGHten trial (full analysis set). **a** Height SDS. Across enliGHten visits, the number of participants with height SDS data decreased predominantly due to participants completing the trial. **b** IGF-1 SDS. Light blue box represents the protocol-specified target range of IGF-1 SDS 0–2. **c** Lonapegsomatropin dose. Week 0 represents the start of the enliGHten trial.

Table 2. Treatment completers: demographics and key data at baseline and at the last visit

Baseline demographics in enliGHten	Variable	Treatment completers (n = 81)
Age, years	Mean (SD) Min, max	13.3 (1.8) 8.8, 17.4
Sex, n (%)	Male	66 (81.5)
Height SDS	Mean (SD)	−1.6 (0.7)
IGF-1 SDS	Mean (SD)	0.8 (1.5)
Tanner stage, n (%)	Stage I Stage II Stage III Stage IV Stage V	22 (30.1) 17 (23.3) 28 (38.4) 6 (8.2) 0
Key data at the last visit in enliGHten	**Variable**	**Treatment completers (n = 81)**
Age, years	Mean (SD) Min, max Male, mean (SD) Female, mean (SD)	16.5 (1.4) 13.0, 18.6 16.8 (1.0) 14.5 (1.0)
Tanner stage, n (%)	Stage I Stage II Stage III Stage IV Stage V	0 0 0 23 (28.4) 58 (71.6)
Met or exceeded average parental height SDS, n (%)		48 (59.3)
Duration of total lonapegsomatropin treatment (heiGHt or fliGHt plus enliGHten), years	Mean (SD) Min, max	3.2 (1.1) 0.5, 5.3

In the enliGHten trial, mean (SD) height SDS continued to increase over time, approaching 0 SDS, which corresponds to the mean height for children of average stature (adjusted for sex and age). By year 4 of the enliGHten trial (Week 208), the mean (SD) height SDS for participants remaining in the trial at this time point (n = 148) was −0.39 (0.90) (Fig. 1a).

Weekly average IGF-1 SDS mean levels remained within the protocol-specified target range of 0–2 SDS over time in the trial for the full analysis set (Fig. 1b). The starting dose of lonapegsomatropin in the phase 3 trials for children with GHD (heiGHt and fliGHt) was 0.24 mg hGH/kg/week. Over the course of the enliGHten trial, the mean lonapegsomatropin dose slightly declined to 0.22 mg hGH/kg/week at week 208 (n = 101) (Fig. 1c). Overall, 42% of participants had 1 or more dose decreases due to elevated IGF-1 SDS. The mean (95% CI) incidence of dose decrease due to IGF-1 was 0.3 (0.22–0.32) per year.

Treatment Completers

During the course of the enliGHten trial, 81 participants completed treatment with lonapegsomatropin due to investigator's assessment that GH treatment for pediatric GHD was no longer necessary. This included participants with evidence of final or near final height on bone age X-ray. Treatment completers were mean (SD) chronological age 13.3 (1.8) years at the start of the enliGHten trial, ranging from 8.8 to 17.4 years, and at their last visit, mean (SD) age was 16.5 (1.4) years and ranged from 13.0 to 18.6 years. All treatment completers were Tanner stage IV (28.4%) or V (71.6%) at the last visit (Table 2). Among treatment completers, the lonapegsomatropin treatment duration across heiGHt, fliGHt, and enliGHten was a median of 3.3 years (maximum 5.3 years).

When data were summarized for each treatment completer's last visit, mean (SD) height SDS was −0.36 (0.74), which exceeded the mean (SD) average parental height SDS for treatment completers of −0.44 (0.76)

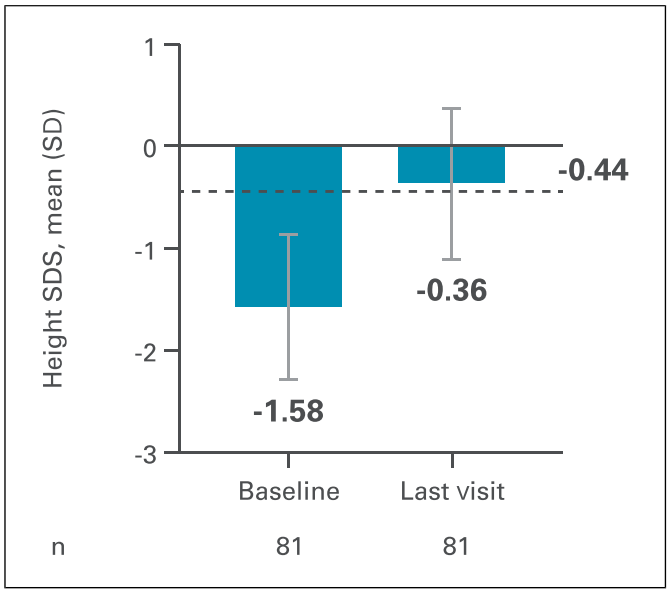


Fig. 2. Height SDS at enliGHten baseline and enliGHten last visit for treatment completers. Dashed line indicates mean average parental height SDS (average parental height = height SDS_{mother} + height SDS_{father}]/2) for treatment completers (n = 81, −0.44).

(Fig. 2). Mean height SDS (SD) at the last visit for treatment completers was similar for males (n = 66, −0.39 [0.81]) and females (n = 15, −0.35 [0.73]). The change in height SDS from enliGHten baseline to participants' final visit was mean (SD) 1.22 (0.71). At participants' last visit, 59.3% of treatment completers met or exceeded their individual average parental height SDS.

Post hoc Analyses

Post hoc longitudinal analysis of AHV data across the heiGHt, fliGHt, and enliGHten trials for the full analysis set summarized by age and year of lonapegsomatropin treatment for male and female participants are depicted in Figure 3a and b, respectively. Higher growth rates were seen in toddlers up to approximately 4 years old and in adolescents around 14–16 years, with a tapering off as epiphyseal closure approached around 17–18 years of age, as the majority of the participants were males. The highest AHV was noted during the first year of lonapegsomatropin treatment, in line with typical catch-up growth patterns after GH treatment initiation [13].

Consistent with literature describing increased IGF-1 concentrations during puberty [14], a post hoc analysis revealed a trend of an increase in weekly average IGF-1 SDS mean with more advanced Tanner stage while remaining within the protocol-specified target range of 0 to +2 SDS (Fig. 4a). The mean lonapegsomatropin dose remained relatively similar to the starting dose of 0.24 mg hGH/kg/week across all Tanner stages, with a slight decrease detectable during Tanner stages IV and V (Fig. 4b). Despite lower weight-based doses in higher Tanner stages, robust growth as measured by AHV was observed across all Tanner stages (Fig. 4c).

Safety

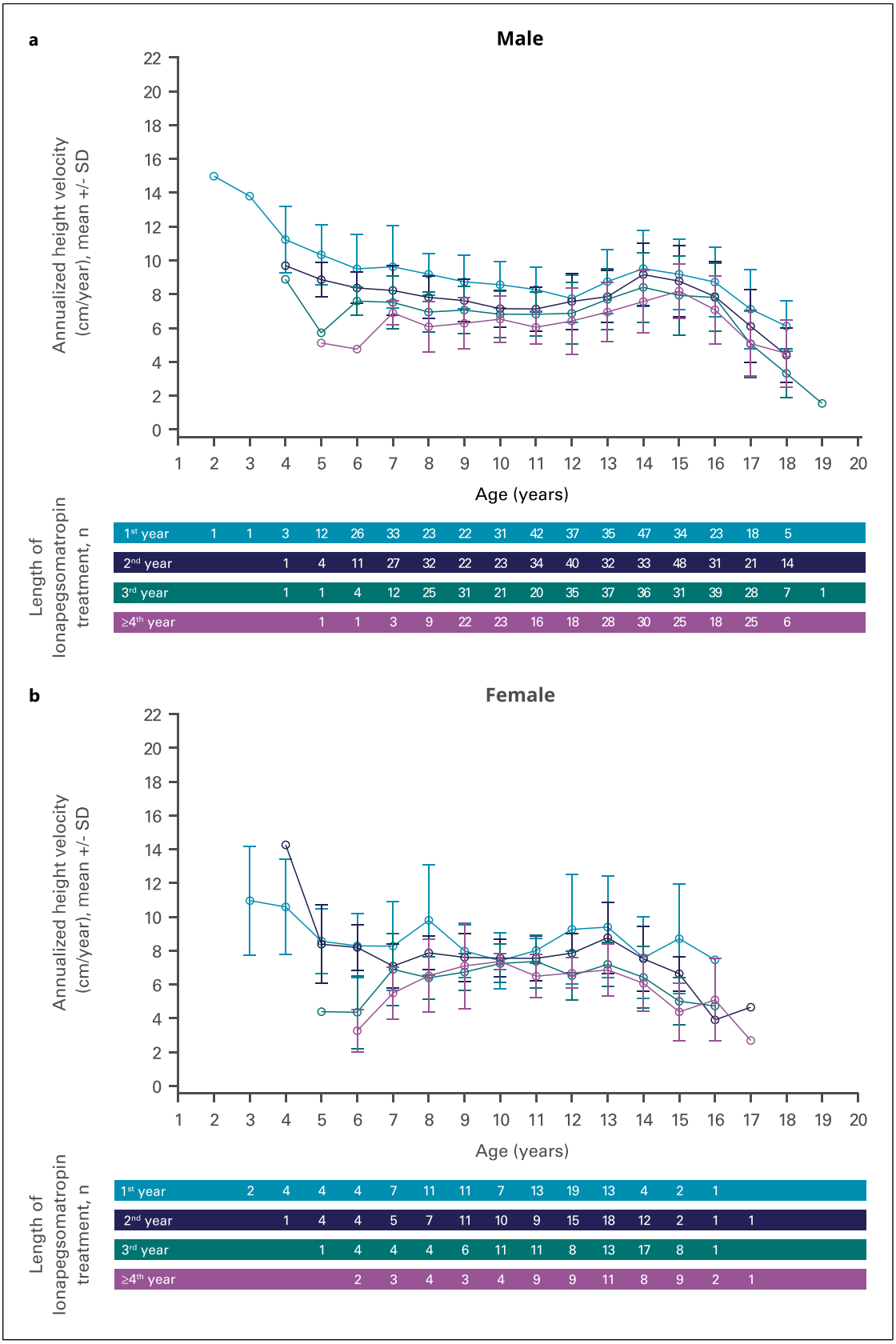
During the enliGHten trial, 75.8% (n = 226) of participants experienced treatment-emergent AE (TEAEs) at any time during the trial. The most commonly reported TEAEs (occurring in ≥5% of participants) are shown in Figure 5a. Most TEAEs were assessed as mild (40.9%) or moderate (31.2%); 11 (3.7%) participants experienced TEAEs assessed as severe, but none of these were assessed as related to study drug.

Overall, 25 participants experienced TEAEs assessed as related to study drug by the investigator. The most common were general disorders and administration site conditions (2.7%), in which 8 participants experienced a total of 12 injection site reactions that were all mild or moderate and resolved prior to the end of study. This was followed by musculoskeletal and connective tissue disorders (2.3%), in which 2 participants experienced scoliosis events that were assessed as mild or moderate. There were no cases of intracranial hypertension or pancreatitis.

There were 21 (7%) participants who experienced a total of 35 SAEs. All 35 events were assessed by the investigator as not related to study drug. Overall, no AEs led to the discontinuation of lonapegsomatropin treatment. Evaluation of the ratio of bone age to chronological age in the enliGHten trial revealed no evidence of accelerated skeletal maturation throughout long-term lonapegsomatropin treatment, with mean ratios remaining below 1 (Fig. 5b).

Clinical laboratory parameters remained stable over the course of the trial. Lipid profiles, including total cholesterol, LDL, HDL, and triglycerides, showed no significant changes. Mean HbA1c, cortisol, and thyroxine stayed within their respective reference ranges throughout the trial. Mean body mass index (BMI) SDS remained within the normal range, with values trending toward 0 over time (online suppl. Fig. 2).

The rate of injection site reactions was low for lonapegsomatropin, with improved tolerability with autoinjector administration compared to vial/syringe administration. Exposure-adjusted rates for local tolerability assessments (swelling, redness, bruising, itching)



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showed that 7.1% of lonapegsomatropin vial/syringe injections were associated with a reaction vs. 1.3% of lonapegsomatropin auto-injector injections.

The incidence of anti-drug antibodies was low and transient throughout lonapegsomatropin treatment in the heiGHt, fliGHt, and enliGHten trials, and no neutralizing antibodies were detected. Overall, 25 participants (8.4%) had detectable antibodies after the first dose of lonapegsomatropin for any of the 3 types of antibodies assessed (anti-hGH, anti-mPEG, and anti-lonapegsomatropin). Anti-drug antibody incidence decreased over time after starting lonapegsomatropin treatment, dropping to zero positive samples (out of 236 samples) by week 156 of treatment, a single detectable positive sample (out of 93 samples) at week 247, and none following that time point out to week 312.

Discussion

The enliGHten trial represents the first completed Phase 3 extension trial in pediatric GHD for an FDA- and EC-approved LAGH product and extends our understanding of lonapegsomatropin therapy in pediatric GHD by providing long-term outcomes. Height outcomes, growth patterns, dose requirements, and safety profiles were favorable in children with GHD who were treated with lonapegsomatropin over an extended period. The results of enliGHten reinforce the efficacy and safety of lonapegsomatropin observed in the heiGHt and fliGHt trials.

Treatment with lonapegsomatropin resulted in closing the height gap between participants with GHD and children of average stature. In the overall trial population, mean height SDS was −0.39 at the 4-year visit (Week 208) in the enliGHten trial, well within the range of average stature children (−2.0 to +2.0 SDS). Of note is that lonapegsomatropin therapy proved to be efficacious in supporting participants to approach or exceed their genetic height potential. Among treatment completers, 59.3% met or exceeded their individual average parental height SDS.

Robust growth was observed with up to 6 years of treatment with lonapegsomatropin in the pediatric GHD clinical program across the heiGHt, fliGHt, and enliGHten trials. Analysis of AHV throughout the childhood growing years demonstrated the expected pattern of achieving the highest AHVs following GH treatment initiation [13]. A noticeable acceleration in growth was observed during puberty in patients receiving lonapegsomatropin treatment, suggesting that the pubertal growth spurt was maintained. To the best of our knowledge, this is the first report to describe growth patterns in children with GHD across various ages and pubertal stages during LAGH therapy.

Robust growth rates were observed in adolescents across Tanner stages, without a need for higher weight-based dosing. The enliGHten trial followed children through puberty, with treatment completers exiting the trial at Tanner IV or V. Interestingly, although clinicians have historically considered the need for higher doses during puberty [15, 16], in the enliGHten trial, on average, no dose increases (on a mg/kg/week basis) were observed when progressing through puberty to maintain effects on growth. Slightly lower weight-based doses were observed for more advanced Tanner stages compared to pre-pubertal weight-based doses.

As lonapegsomatropin has a linear relationship between dose and IGF-1 SDS, and IGF-1 levels can be assessed after at least 2 doses [17], dose reductions were able to be carried out appropriately in the long-term enliGHten trial [18, 19]. IGF-1 was sampled 4–6 days post-dose during the trial as sampling at day 4.5 corresponds to weekly average IGF-1 levels. In clinical practice, where sampling may occur outside this window, an algorithm is available to convert the measured value into the weekly average value [19].

The safety profile of lonapegsomatropin across the heiGHt, fliGHt, and enliGHten trials was aligned with the well-characterized safety of somatropin, with AEs predominantly reflecting common childhood illnesses. Lonapegsomatropin was associated with a low incidence of anti-drug antibodies and absence of anti-hGH neutralizing antibodies, with no safety signal associated with antibodies to hGH, mPEG, or lonapegsomatropin. Additionally, observed glucose stability and age-appropriate bone maturation further support the long-term safety profile of lonapegsomatropin. Injection site reactions have been a key historical concern with LAGH formulations [20]. Importantly, rates of injection site reactions with lonapegsomatropin were low and comparable to those observed with daily somatropin delivery via vial and

Fig. 3. AHV during lonapegsomatropin treatment throughout childhood. AHV by age and year of lonapegsomatropin treatment (across the heiGHt, fliGHt, and enliGHten trials) for males (**a**) and females (**b**) in the full analysis set. The number of participants with height assessments for each age and year of lonapegsomatropin treatment is shown below the graph.

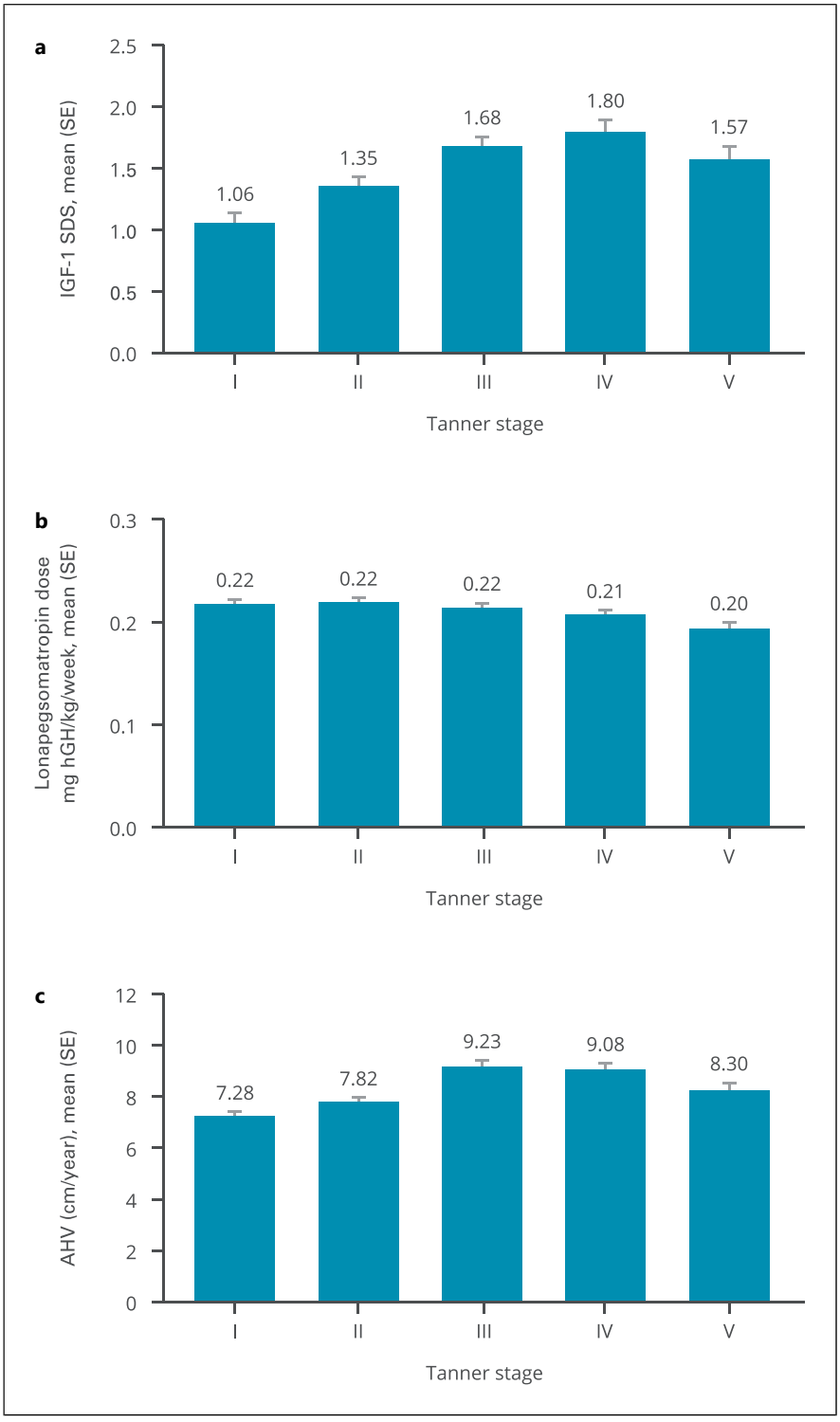

Fig. 4. Tanner stage analysis. IGF-1 SDS (**a**), lonapegsomatropin dose (**b**), and AHV (**c**) were estimated by Tanner stage across heiGHt, fliGHt, and enliGHten using a mixed effects repeated measures model with the outcome as the dependent variable, sex as fixed effects, age, Tanner stage, and duration of exposure on lonapegsomatropin as time varying covariates, and random intercept within participant as a random effect. For AHV, assessments at the end of 1, 2, 3, and 4 years of lonapegsomatropin treatment were included in the analysis. IGF-1 values for the heiGHt lonapegsomatropin group were model derived and represented the average IGF-1 SDS.

syringe and were further decreased in participants who switched to the auto-injector.

Going forward, the enliGHten clinical trial findings will be further validated through the SkybriGHt registry study in the USA (NCT05820672) and the SkyPASS study in the USA and Europe (NCT05775523/EUPAS50671), which will expand available data regarding longer-term treatment outcomes with lonapegsomatropin in clinical

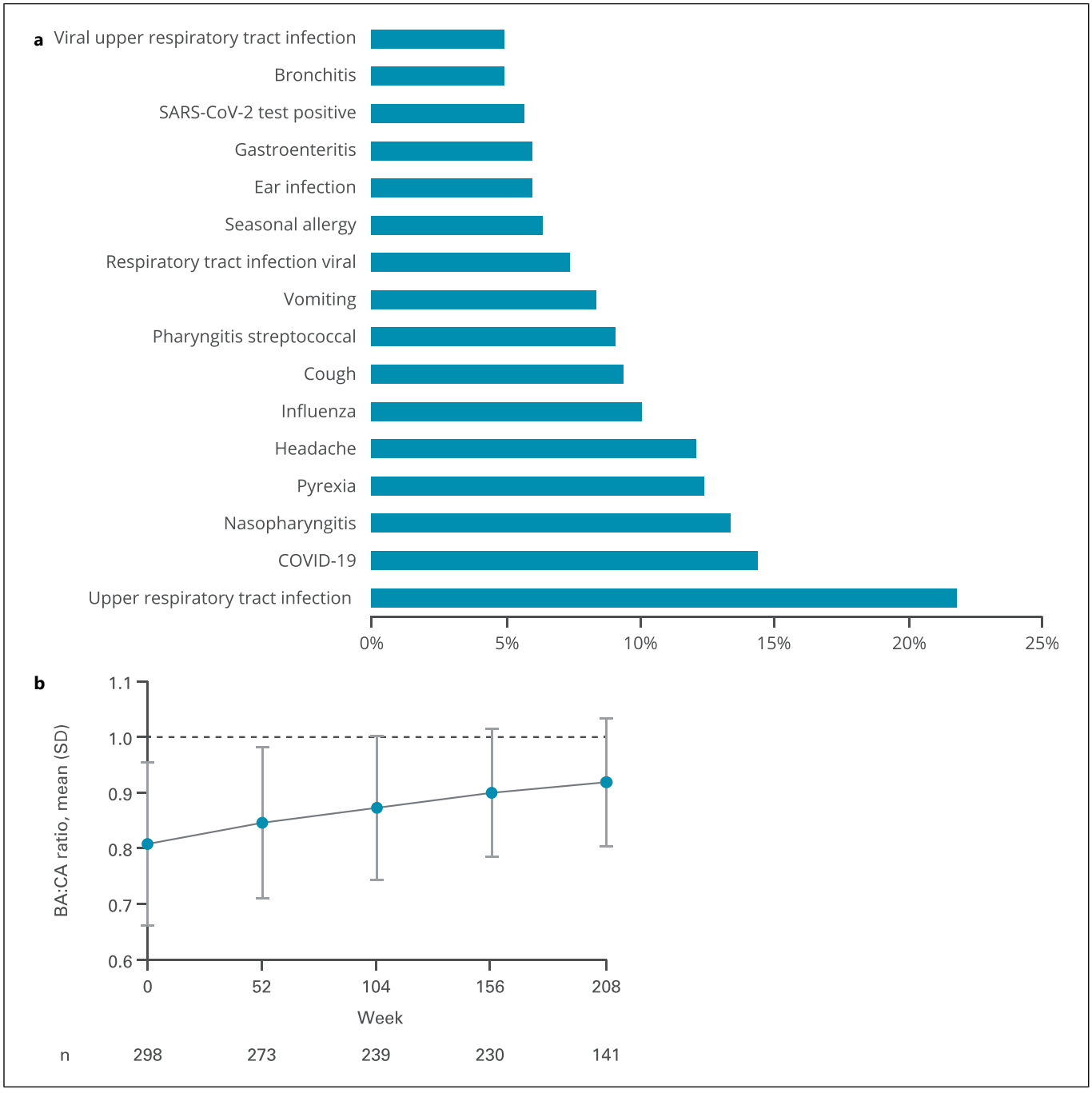

Fig. 5. Safety assessments during the enliGHten trial. **a** TEAEs (regardless of investigator assessment of causality) reported in ≥5% of participants (N = 298) in the enliGHten trial full analysis set. **b** Bone age:chronological age (BA:CA) ratio during the enliGHten trial for the full analysis set. COVID-19, coronavirus disease-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

practice. These studies will provide valuable insights into the real-world effectiveness of lonapegsomatropin in children with GHD.

The enliGHten trial demonstrated long-term safety and efficacy using lonapegsomatropin for the treatment of pediatric GHD, including a subset of participants who

completed GH treatment during the trial. Lonapegsomatropin demonstrated sustained efficacy and a safety profile consistent with somatropin. The potential for improved treatment outcomes with increased adherence with a once-weekly injection makes lonapegsomatropin a promising option for enhancing growth outcomes and quality of life for children with GHD.

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Statement of Ethics

The Principal Investigator at each site was responsible for obtaining approval from the appropriate regional Institutional Review Board (IRB), Human Research Ethics Committee (HREC), or Independent Ethics Committee (IEC) for the final protocol, sponsor-approved informed consent form and subject information sheet (if applicable), and any advertisements to recruit subjects. The protocol was approved by a Local Institutional Review Board, Independent Ethics Committee, or Human Research Ethics Committee prior to trial initiation, and the study was conducted in accordance with the Declaration of Helsinki. All parents/legal guardians provided written informed consent prior to patient participation in any patient-specific procedures. The full list of sites and ethics boards can be found in the online supplementary Table.

Conflict of Interest Statement

E.V. received research funding from Ascendis Pharma, OPKO, and Janssen; and honoraria from Sandoz, Eli Lilly, and Novo Nordisk. P.H. received honoraria: Novo Nordisk and Eli-Lilly. P.S.T. received research funding from Ascendis, Pfizer, Opko, Zealand, Rezolute, Spruce; expert testimony from Johnson and Johnson; travel, accommodations, and expenses from Rezolute. E.M.A. received travel, accommodations, and expenses from Berlin Hemi Menarini Pharmaceutical Company and also has conference attendance. M.K.-S. received research funding from Ascendis Pharma. A.K.M. received honoraria from Ascendis, Novo Nordisk, Pfizer; on the advisory board of Ascendis, Novo Nordisk, Pfizer; consulted for Ascendis and Novo Nordisk; has been speaker bureau for Ascendis, Novo Nordisk; and received research funding from Ascendis, Novo Nordisk, OPKO, and Pfizer; U.M.N. has nothing to disclose. M.M., C.Z., S.G.A., E.A.H., A.S.K., and A.D.S. are employees of Ascendis Pharma Inc.

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Author Contributions

A.K.M., P.S.T., U.M.N., E.V., O.M., E.M.A., M.K.-S., K.A.W., and P.H.: acquisition, analysis, interpretation of data; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work. M.M., C.Z., S.G.A., E.A.H., A.S.K., and A.D.S.: conception or design of the work; or acquisition, analysis, or interpretation of data; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

Data Availability Statement

Some or all data sets generated during and/or analyzed during the current study are not publicly available as they contain data that may compromise the privacy of research participants, but are available from the corresponding author, A.D.S., on reasonable request.

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